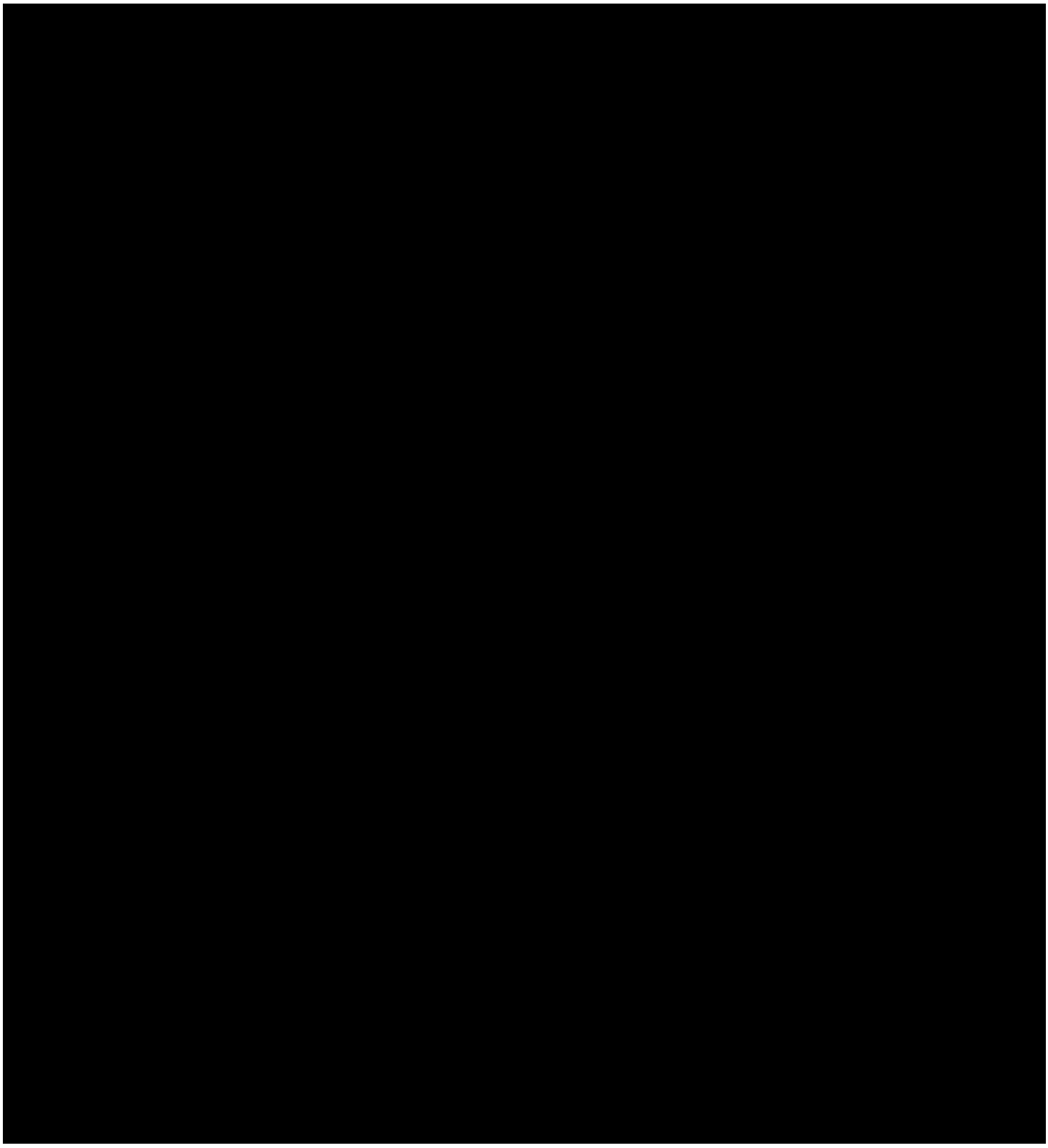
[redacted]

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection (DAXI for Injection) for the Combined Treatment of Upper Facial Lines (Glabellar Lines, Dynamic Forehead Lines and Lateral Canthal Lines)
Protocol Number:	1920201
Document Type:	Protocol
Study Phase:	Phase 2
Short Title:	Efficacy and Safety of DaxibotulinumtoxinA (DAXI) for Injection for Treatment of Upper Facial Lines
Sponsor:	Revance Therapeutics, Inc. 7555 Gateway Boulevard Newark, CA 94560
Version:	Original Protocol, 25 October 2019

This study will be conducted in compliance with the obligations detailed in this protocol and all applicable regulations and guidelines (e.g., International Conference on Harmonisation [ICH] and Good Clinical Practices [GCP]).



INVESTIGATOR'S AGREEMENT

I have carefully read the protocol entitled: "**A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection (DAXI for Injection) for the Combined Treatment of Upper Facial Lines (Glabellar Lines, Dynamic Forehead Lines and Lateral Canthal Lines)**" and,

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the trial personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the trial protocol.

I agree to conduct this clinical trial according to the attached protocol, in compliance with all applicable laws and regulations, and in accordance with the ethical principles stipulated in the Declaration of Helsinki.

Investigator Signature	**Date**
Printed Name	
Institution Name	
Address	
City, State, Postal Code, Country	**Phone Number**

Table of Contents

List of Tables

[redacted]

LIST OF ABBREVIATIONS

[redacted]	[redacted]
AE	adverse event
CI	confidence interval
DAXI	DaxibotulinumtoxinA
eCRF	electronic case report form
FASE	Facial Age Self Evaluation
FDA	Food and Drug Administration
FHL	forehead lines
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GL	glabellar lines
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA-FWS	Investigator Global Assessment Frown Wrinkle Severity
IGA-FHWS	Investigator Global Assessment Forehead Wrinkle Severity
IGA-LCWS	Investigator Global Assessment Lateral Canthal Wrinkle Severity
IM	intramuscular(ly)
IP	investigational product
IRB	Institutional Review Board
kDa	kilodalton
LCL	lateral canthal lines
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
NSAID	nonsteroidal anti-inflammatory drug
PFWS	Patient Frown Wrinkle Severity
PFHWS	Patient Forehead Wrinkle Severity
PHI	protected health information
PI	Principal Investigator
PLCWS	Patient Lateral Canthal Wrinkle Severity
PNA	Patient Naturalness Assessment
PT	prothrombin time
SAE	serious adverse event
SNAP-25	25 kDa synaptosome associated protein

SOA	schedule of assessments
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
U	units
UPT	urine pregnancy test
WOCBP	women of childbearing potential

1. Protocol Summary

1.1. Synopsis

Title

A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection (DAXI for Injection) for the Combined Treatment of Upper Facial Lines (Glabellar Lines, Dynamic Forehead Lines and Lateral Canthal Lines)

Study Description:

This is a Phase 2, multicenter, open-label, single-arm study to evaluate the safety and efficacy of DaxibotulinumtoxinA for injection (DAXI for injection) in the treatment of glabellar lines (GL), dynamic forehead lines (FHL), and lateral canthal lines (LCL).

Approximately 48 subjects (18 years of age and above) with moderate to severe GL, FHL, and LCL (all assessed at maximum contraction) will be screened for eligibility and enrolled to receive a single treatment of DAXI for injection to be injected into 5 GL sites, 4 FHL sites, and 3 LCL sites per side (total of 6 LCL sites).

All subjects will be assigned to receive DAXI for injection.

The principal investigator (PI) at each clinical site will utilize a standard 5-point injection paradigm when injecting GL-complex (procerus and corrugator muscles), a 4-point injection paradigm when injecting the frontalis muscle, and a 3 point-injection paradigm when injecting the lateral canthal area bilaterally.

The primary objective of this study is to determine the efficacy and safety of the combined treatment of three upper facial regions with DAXI for injection.

The efficacy response for GL is the proportion of subjects reporting an improvement in severity defined as achieving a score of 0 (none) or 1 (mild) at Week 4, at maximum contraction (maximum frown) on the Investigator Global Assessment Frown Wrinkle Severity (IGA-FWS) scale and separately, on the Patient Frown Wrinkle Severity (PFWS) scale.

The efficacy response for FHL is the proportion of subjects reporting an improvement in severity defined as achieving a score of 0 (none) or 1 (mild) at Week 4, at maximum contraction (maximum eyebrow elevation) on the Investigator Global Assessment Forehead Wrinkle Severity Scale (IGA-FHWS) scale and separately, on the Patient Forehead Wrinkle Severity (PFHWS) scale.

The efficacy response for LCL is the proportion of subjects reporting an improvement in severity defined as achieving a score of 0 (none) or 1 (mild) at Week 4, at maximum contraction (maximum smile effort) on the Investigator Global Assessment Lateral Canthal Wrinkle Severity (IGA-LCWS) scale and separately, on the Patient Lateral Canthal Wrinkle Severity (PLCWS) scale.

Objectives:

Primary Objective:

- To evaluate the efficacy and safety of DAXI for injection for the combined treatment of GL, FHL, and LCL.

Endpoints:

Key Endpoints

- The proportion of subjects achieving a score of 0 (none) or 1 (mild) in GL severity at maximum contraction at Week 4 as assessed by the IGA-FWS
- The proportion of subjects achieving a score of 0 (none) or 1 (mild) in FHL severity at maximum contraction at Week 4 as assessed by the IGA-FHWS
- The proportion of subjects achieving a score of 0 (none) or 1 (mild) in LCL severity at maximum contraction at Week 4 as assessed by the IGA-LCWS

[redacted]

Safety Evaluations:

- Vital signs
- Physical examination
- [redacted]
- Injection site evaluation
- Concomitant therapies/medications
- Clinical laboratory tests (hematology, serum chemistry, prothrombin time [PT], urinalysis)
- [redacted]
- Adverse events (AEs)
- Incidence, severity, and relationship to study drug of treatment-emergent AEs (TEAEs) and serious adverse events (SAEs) during the overall study duration.

Evaluations:

- FACE-Q™
  - FACE-Q™ Appraisal of Lines: Overall
  - FACE-Q™ Appraisal of Lines: Forehead
  - FACE-Q™ Appraisal of Lines: Between Eyebrows
  - FACE-Q™ Appraisal of Lines: Crow's Feet Lines
  - FACE-Q™ Satisfaction with Forehead and Eyebrows
  - FACE-Q™ Psychological Function
  - FACE-Q™ Satisfaction with Outcome
- Facial Age Self Evaluation (FASE)
- Global Aesthetic Improvement Scale (GAIS-Subject and Investigator)
- Subject Global Satisfaction with Treatment
- Patient Naturalness Assessment (PNA)
- Photography of treatment areas including standardized image capture of right, left, and frontal views at rest and at maximum contraction (frown, smile, and forehead elevation); and standardized video capture of frontal and oblique views at maximum contraction (frown, smile, and forehead elevation).

Study Population:

Approximately 48 male and female subjects aged 18 and over years of age.

Inclusion Criteria:

To be eligible for participation, subject must:

1. Provide written informed consent consistent with ICH-GCP guidelines and local laws, including authorization to release health information, signed prior to any study procedures being performed
2. Be outpatient, male or female subjects, in good general health, 18 years of age or older
3. Have a score of moderate (2) or severe (3) GL during maximum contraction as assessed by the IGA-FWS and PFWS
4. Have a score of moderate (2) or severe (3) FHL during maximum contraction as assessed by the IGA-FHWS and PFHWS
5. Have a score of moderate (2) or severe (3) LCL at maximum contraction as assessed by the IGA-LCWS and PLCWS (scores must be consistent bilaterally for each scale considered separately)
6. Have sufficient visual acuity without the use of eyeglasses (contact lens use is acceptable) to accurately assess their facial wrinkles
7. All WOCBP must use an effective method of birth control throughout the study, (e.g., oral contraceptive pill, injection, implant, patch, vaginal ring, intrauterine coil, intrauterine device, tubal ligation, barrier method) used WITH an additional form of contraception (e.g., sponge, spermicide or condom); true abstinence (i.e. no heterosexual intercourse) or having a vasectomized partner is considered an acceptable method of contraception
8. Able to understand the requirements of the study and be willing and able to follow all study procedures, attend all scheduled visits, comprehend and complete the questionnaires without outside assistance and successfully complete the study

Exclusion Criteria:

Subjects will not be eligible for study participation if they meet any of the following criteria:

1. Any evidence of facial nerve deficiency
2. Evidence that frontalis activity is required to maintain eyelid position and/or masking underlying lid or brow ptosis
3. Active skin disease, infections, or inflammation at the injection sites
4. Upper or lower lid blepharoplasty or brow lift or other periorbital or forehead surgery
5. Undergone any procedure in the past 12 months prior to screening that may affect the upper facial region, such as an ablative laser skin resurfacing or soft tissue augmentation in the forehead, glabellar, brow, and infrabrow regions; or any procedure that may affect the lateral canthal regions, such as an ablative laser skin resurfacing or soft tissue augmentation above the oral commissures
6. Use of facial fillers, barbed lifting sutures, any product that affects skin remodeling, or any product that may cause an active dermal response in the treatment areas in the past 12 months prior to screening
7. Previous treatment with botulinum toxin type A in the face in the past 6 months prior to screening
8. Has had treatment with >200 U of any botulinum toxin anywhere else in the body outside of the face in the past 6 months prior to screening
9. Use of prescription oral retinoids in the past 6 months prior to screening

[redacted]

[redacted]

Phase:	2
Description of Sites Enrolling Subjects:	The study will be conducted at up to 8 sites in the United States and Canada.
Description of Study Intervention:	[redacted]
Subject Duration:	Up to 38 weeks, including 2 weeks for screening

[redacted]

[redacted]

2. Introduction

Visible signs of facial aging include the formation of facial lines and folds, a decline in skin quality, an increase in skin pigmentation, and, in women, post-menopausal loss or redistribution of soft tissue volume and bone. Forehead lines (FHL) are produced by the action of the frontalis muscle, a large, thin, vertically-oriented muscle which lifts the eyebrows (Hexsel, 2011; Klein, 2004). The frontalis muscle serves as an antagonist to the glabellar musculature, a natural depressor that is responsible for frowning and associated eyebrow movement. As the eyebrow is considered the aesthetic center of the upper face, FHL can significantly impact the aesthetic appearance of the face, contribute to increased signs of aging and convey unwanted social signals. In addition, the formation of wrinkles at the corners of the eyes, which are referred to as crow's feet lines or lateral canthal lines (LCL), are one of the primary signs of aging that can negatively impact the assessment of a person's age. These dynamic lines appear during facial muscle contractions, like smiling and squinting, and over time can become permanent or static, meaning that they are still visible when without muscle contraction (Kane, 2015).

Minimally-invasive injectable treatments have become the most common procedure worldwide (Carruthers, 2015) with an increase in frequency over the last decade since the first approval of botulinum neurotoxin type A (Botox Cosmetic [onabotulinumtoxinA] UPSI, Allergan, Inc. 2013). This is largely the result of years of experience of patients and injectors, and a favorable risk-benefit profile.

Botulinum neurotoxin is produced by *Clostridium botulinum*, which is a gram-positive, spore-forming, anaerobic bacterium, which can both cause disease (e.g., botulism), as well as treat it (e.g., dystonia) (Simpson, 2004). There are 7 distinct serotypes of botulinum toxin (A-G), and only types A and B have established clinical uses due to a longer duration of action compared to the other types (De Boulle, 2007). Botulinum neurotoxin type A inhibits acetylcholine release at the neuromuscular junction, which prevents muscle contractions in injected muscles. The onset of muscle weakening typically begins within 48 hours after treatment and usually lasts between 3 and 4 months, although some patients have reported shorter or longer durations (Carruthers, 2015; De Boulle, 2007).

A large, 12-month, phase 3 study was conducted to examine simultaneous treatment of FHL, GL, and LCL with onabotulinumtoxinA (De Boulle, 2018). This study enrolled 787 subjects, of which 313 subjects received onabotulinumtoxinA 64 U, 318 subjects received onabotulinumtoxinA 40 U, and 156 subjects received placebo. In subjects receiving 64 U and 40 U of onabotulinumtoxinA, a statistically significant improvement ($p < 0.001$, for both doses compared with placebo) in the appearance of FHL was observed at the 30-day timepoint and maintained, when compared with placebo, through Day 180. In subjects achieving a 2-point improvement in FHL severity from baseline, the investigator assessment of FHL improvement was statistically significant at all timepoints through Day 180. Significantly more subjects who received 64 U onabotulinumtoxinA achieved a rating of none or mild, compared to 40 U and compared to placebo, as assessed by the investigator, at Day 30 for FHL and GL severity ($p < 0.001$ for both comparisons). Additionally, eye-related TEAEs were very low; there were 2 cases each of eyelid and brow ptosis (0.6%) at the 64 U dose and 5 cases (1.6%) and 6 cases (1.9%) of eyelid and brow ptosis, respectively, at the 40 U dose. The safety profile of onabotulinumtoxinA is well established and enhanced in this study by simultaneous treatment of FHL and GL, which has been shown to reduce the incidence of ptosis by stabilizing the elevator muscle.

As both men and women gain increased awareness of the recognition of aesthetic treatment options available to address the signs of facial aging, and as treatment becomes more widely used and accepted, it is important to continue examining the potential benefits of such treatments in the context of unmet clinical need, improved self-satisfaction, and increased demand. Aesthetic products and procedures, while not medically necessary, can significantly improve social and psychological functioning, as well as self-satisfaction, which can have a meaningful and significant impact on daily life and patient well-being (Fagien, 2008).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of DAXI for injection may be found in the Investigator's Brochure.

3. Objectives and Endpoints

All efficacy endpoints will be assessed using the last available assessment prior to treatment on Day 1 as baseline.

Primary Objective:

- To evaluate the efficacy and safety of DAXI for injection for the combined treatment of GL, FHL, and LCL

Safety Evaluations

- Vital signs
- Physical examination
- Injection site evaluation
- Concomitant therapies/medications
- Clinical laboratory tests (hematology, serum chemistry, prothrombin time [PT], urinalysis)
- [redacted]
- Adverse events (AEs)
- Incidence, severity, and relationship to study drug of treatment-emergent AEs (TEAEs) and serious adverse events (SAEs) during the overall study duration.

Evaluations

- FACE-Q™
  - FACE-Q™ Appraisal of Lines: Overall
  - FACE-Q™ Appraisal of Lines: Forehead
  - FACE-Q™ Appraisal of Lines: Between Eyebrows
  - FACE-Q™ Appraisal of Lines: Crow's Feet Lines
  - FACE-Q™ Satisfaction with Forehead and Eyebrows
  - FACE-Q™ Satisfaction with Outcome
  - FACE-Q™ Psychological Function
- Facial Age Self Evaluation (FASE)
- Global Aesthetic Improvement Scale (GAIS-Subject and Investigator)
- Subject Global Satisfaction with Treatment
- Patient Naturalness Assessment (PNA)
- Photography of treatment areas including standardized image capture of right, left, and frontal views at rest and at maximum contraction (frown, smile, and forehead elevation); and standardized video capture of frontal and oblique views at maximum contraction (frown, smile, and forehead elevation).

3.1. Overall Design

This is a phase 2, multicenter, open-label, dose-escalation study to evaluate the safety and efficacy of DAXI for injection for the treatment of subjects with moderate to severe GL, FHL and LCL. This study will be conducted at 8 sites in the United States and Canada.

Approximately 48 subjects (18 years of age and above) with moderate to severe GL, FHL and LCL (all assessed at maximum contraction) will screened for eligibility and enrolled to receive DAXI for injection after providing informed consent. [redacted]

The total study duration will be up to 38 weeks, including up to 2 weeks for screening. After treatment on Day 1, subjects will be followed for a minimum of 24 weeks and up to 36 weeks. Subjects will complete the study at Week 36 or earlier (on or after Week 24), if the severity scores for GL, FHL, and LCL return to baseline (Day 1 pretreatment) or worse based on both the investigator and subject evaluations. Subjects who return to baseline or worse in GL, FHL, and LCL severity scores prior to Week 36 will complete a Final Evaluation Visit upon the site confirming their status as an early completer, by referring to baseline evaluations.

3.4. Visit Schedule

A screening visit will be conducted up to 2 weeks prior to enrollment, and subjects will receive investigational product at baseline (Day 1). A follow-up safety phone call will be conducted at

Week 1. Post-treatment on-site follow-up visits will occur at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36. The total study duration will be up to 38 weeks, including up to a 2-week screening period. For safety, subjects will be followed after treatment for a minimum of 24 weeks and up to 36 weeks. On or after Week 24, if the severity scores for GL, FHL, and LCL return to baseline (Day 1 pretreatment) or worse based on both the investigator and subject evaluation, subjects will complete the study and will have a Final Evaluation Visit.

Subjects will be evaluated for GL severity on the IGA-FWS and the PFWS at rest and at maximum frown, for FHL severity using the IGA-FHWS and PFHWS at rest and at maximum eyebrow elevation, and for LCL severity using the IGA-LCWS and PLCWS at rest and at maximum smile. The IGA-FWS, PFWS, IGA-FHWS, PFHWS, IGA-LCWS and PLCWS have all been validated by Revance.

4. Study Population

Approximately 48 female or male subjects, 18 of age and older with moderate to severe GL, FHL, and LCL at maximum contraction will be enrolled. Subjects must meet all the inclusion criteria and none of the exclusion criteria to be eligible for the study.

4.1. Inclusion Criteria

To be eligible for participation, subjects must:

1. Provide written informed consent consistent with ICH-GCP guidelines and local laws, including authorization to release health information, signed prior to any study procedures being performed
2. Be outpatient, male or female subjects, in good general health, 18 years of age or older
3. Have a score of moderate (2) or severe (3) GL during maximum frown as assessed by the IGA-FWS and PFWS
4. Have a score of moderate (2) or severe (3) FHL during maximum contraction (eyebrow elevation) as assessed by the IGA-FHWS and PFHWS
5. Have a score of moderate (2) or severe (3) LCL at maximum smile effort as assessed by the IGA-LCWS and PLCWS (scores must be consistent bilaterally for each scale considered separately)
6. Have sufficient visual acuity without the use of eyeglasses (contact lens use is acceptable) to accurately assess their facial wrinkles
7. All WOCBP must use an effective method of birth control throughout the study, (e.g., oral contraceptive pill, injection, implant, patch, vaginal ring, intrauterine coil, intrauterine device, tubal ligation, barrier method) used WITH an additional form of contraception (e.g., sponge, spermicide or condom); true abstinence (i.e. no heterosexual intercourse) or having a vasectomized partner is considered an acceptable method of contraception

8. Able to understand the requirements of the study and be willing and able to follow all study procedures, attend all scheduled visits, comprehend and complete the questionnaires without outside assistance and successfully complete the study

4.2. Exclusion Criteria

Subjects will not be eligible for study participation if they meet any of the following criteria:

1. Any evidence of facial nerve deficiency
2. Evidence that frontalis activity is required to maintain eyelid position and/or masking underlying lid or brow ptosis
3. Active skin disease, infections, or inflammation at the injection sites
4. Upper or lower lid blepharoplasty or brow lift or other periorbital or forehead surgery
5. Undergone any procedure in the past 12 months prior to screening that may affect the upper facial region, such as an ablative laser skin resurfacing or soft tissue augmentation in the forehead, glabellar brow, and infrabrow regions; or any procedure that may affect the lateral canthal regions, such as an ablative laser skin resurfacing or soft tissue augmentation above the oral commissures
6. Use of facial fillers, barbed lifting sutures, any product that affects skin remodeling, or any product that may cause an active dermal response in the treatment areas in the past 12 months prior to screening
7. Previous treatment with botulinum toxin type A in the face in the past 6 months prior to screening
8. Has had treatment with >200 U of any botulinum toxin anywhere else in the body outside of the face in the past 6 months prior to screening
9. Use of prescription oral retinoids in the past 6 months prior to screening

4.3. Informed Consent and Authorization to Release Health Information

Written informed consent will be obtained from all subjects before any study-related procedures (including any screening procedures) are performed. The investigator may discuss the trial and the possibility for entry with a potential subject without first obtaining consent. However, a subject wishing to participate must give written informed consent prior to any study-related procedures being conducted, including those performed solely for the purpose of determining eligibility for study participation, and including withdrawal from current medication (if required prior to study entry). The investigator has both the ethical and legal responsibility to ensure that each subject being considered for inclusion in this trial has been given a full explanation of the procedures and expectations for study participation, as well as ample time to decide whether or not to participate and have all questions answered satisfactorily.

The site-specific informed consent must be forwarded to Revance or designee for approval prior to submission to an Investigational Review Board (IRB)/Independent Ethics Committee (IEC) that is registered with the US Department of Health and Human Services or applicable health authority. Each subject will sign the consent form that has been approved by the same IRB/IEC that was responsible for protocol approval. Each informed consent form (ICF) must adhere to the ethical principles stated in the Declaration of Helsinki and will include the elements required by FDA regulations in 21 CFR Part 50, as well as the elements required by ICH GCP guideline, and applicable federal and local regulatory requirements. The consent form must also include a statement that Revance, their designees, and auditing regulatory agencies will have direct access to the subject's records and medical history for study related purposes.

Once the appropriate essential information has been provided to the subject and fully explained by the investigator (or a qualified designee) and it is felt that the subject understands the

implications and risks of participating in the trial, the IRB/IEC approved consent document shall be signed and dated by both the subject and the person obtaining consent (investigator or designee), and by any other parties required by the IRB/IEC or other regulatory authorities. The subject will be given a copy of the signed ICF with the original kept on file by the investigator. All of the above activities must be completed before any study related procedures are conducted (including any screening study procedures).

4.4. Lifestyle Considerations

While enrolled in this study, subjects must agree to refrain from use of the prohibited medications and treatments listed in Section 5.4 for the duration of the study.

4.5. Protocol Deviations

This study will be conducted as described in this protocol, except for emergency situations in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact Revance or designee by telephone at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the investigator and Revance or designee.

4.6. Pregnancy

A female is of childbearing potential UNLESS she is post-menopausal (no menses for 12 consecutive months) or without a uterus and/or both ovaries.

All WOCBP must use an effective method of birth control throughout the study, (e.g., oral contraceptive pill, injection, implant, patch, vaginal ring, intrauterine coil, intrauterine device, tubal ligation, barrier method) used WITH an additional form of contraception (e.g., sponge, spermicide or condom); true abstinence (i.e. no heterosexual intercourse) or having a vasectomized partner is considered an acceptable method of contraception.

Before enrolling WOCBP in this study, investigators must review guidelines about study participation for WOCBP with the subject. The topics should generally include:

- ICF content
- Pregnancy prevention information
- Risks to unborn child(ren)
- Any drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during participation in this study and the potential risk factors for an unintentional pregnancy. The subject must sign the ICF stating that the above-mentioned risk factors for unintentional pregnancy and the consequences were discussed with her.

During the study, all WOCBP should be instructed to contact the investigator immediately (within 24 hours) if pregnancy is suspected (e.g., missed or late menstrual cycle). The investigator, or qualified designee, must immediately notify Revance or designee of any female subject who becomes pregnant any time during study participation, record the information on the Pregnancy Notification Form and send the form to Revance or designee. Subjects will remain enrolled in the study. The investigator will be asked to follow-up with a phone call with the subject periodically throughout the pregnancy and post-delivery as applicable for ongoing health and safety information, as applicable.

If an SAE occurs in conjunction with the pregnancy such as untoward outcome of the pregnancy or of the offspring (spontaneous abortion, or abnormality in the offspring) then the reporting time frame for an SAE must be met and SAE reporting procedures followed. In the event of a normal birth follow-up with the subject will occur with a phone call until the first well baby visit to ensure no SAEs are identified in the neonate, at which time active follow-up to the pregnancy will cease.

5. Study Intervention

The active pharmaceutical ingredient, DaxibotulinumtoxinA, is a purified 150 kilodalton (kDa) botulinum neurotoxin type A, derived from the Hall strain *C. botulinum*. Produced by *C. botulinum* as a single inactive polypeptide chain of 150 kDa, DaxibotulinumtoxinA undergoes proteolytic cleavage by proteases present in the fermentation culture to yield the active di-chain molecule comprised of a 100 kDa heavy chain and a 50 kDa light chain linked via both non-covalent interactions and a disulfide bond (Aoki 2001). The heavy chain plays a role in cell binding, internalization, and translocation of DaxibotulinumtoxinA into nerve cells. The light chain acts as a site-specific metalloprotease causing selective cleavage and inactivation of the 25 kDa synaptosome associated protein (SNAP-25) which is a cell membrane localized component of the vesicular release machinery. This cleavage of SNAP-25 by the light chain of botulinum toxin type A blocks the synaptic vesicle exocytosis and subsequent release of acetylcholine, thus leading to a dose-dependent weakening of the target muscle.

5.1. Study Intervention(s) Administered

This is an open-label, non-randomized study. All subjects will receive DAXI for injection as IM injections. A subject will receive 40 U of DAXI for injection in a standard 5-point injection paradigm in the GL-complex (procerus and corrugator muscles), 32 U of DAXI for injection in a 4-point injection paradigm in the frontalis muscle, and 48 U of DAXI for injection in a 3-point injection paradigm per side in the lateral canthal areas.

[redacted]

[redacted]

[redacted]

5.3. Concomitant Medications/Therapies

Concomitant medications are any prescription or over-the-counter preparations used by subjects during participation in the study. Use of concomitant medications will be recorded on the Concomitant Medications electronic case report form (eCRF) beginning at the Screening Visit (and including anything taken during the previous 30 days) until the Final Evaluation Visit.

The dose and dosing regimen of all prescription and non-prescription therapies and medications, including herbs, vitamins, or other nutritional supplements administered will be documented.

[redacted]

6. Discontinuation of Study Intervention and Subject Discontinuation/Withdrawal

6.1. Subject Discontinuation/Withdrawal from the Study

A subject may voluntarily withdraw from study participation at any time. If the subject withdraws consent and discontinues from the study, the investigator will attempt to determine the reason for discontinuation and record the reason in the subject's study records and on the eCRF. If a subject withdraws consent because of an AE, that AE should be indicated as the reason for withdrawal. In the event of early discontinuation, (i.e., prior to the Final Evaluation) where consent was not withdrawn, the subject should be asked to return to the study center to complete the assessments specified in the Final Evaluation Visit. Subjects who withdraw from the study will not be replaced. Subjects who withdraw from the study, but agree to continued follow-up, must be reconsented by the investigator for this limited participation in the study (unless this situation was adequately described in the original ICF).

If at any time during the study, the investigator determines that it is not in the best interest of the subject to continue, the subject will be discontinued from participation. The investigator can discontinue a subject from study participation at any time if medically necessary or if the subject has failed to follow study procedures or keep follow-up appointments. Appropriate documentation in the subject's study record and eCRF regarding the reason for discontinuation must be completed. Prior to discontinuing a subject from study participation, the investigator will discuss his/her intentions with the Medical Monitor or designee.

All subjects who fail to return to the study center for the required follow-up visits will be contacted by phone to determine the reason(s) why the subject failed to return for the necessary visit or elected to discontinue from the study. If a subject is unreachable by telephone after a

minimum of two documented attempts (one attempt on two different days), a registered letter will be sent requesting that contact be made with the investigator.

Revance has the right to terminate or to stop the study at any time. Should this be necessary, both Revance and the investigator will ensure that proper study discontinuation procedures are completed.

6.2. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

Before a subject is deemed lost-to-follow-up, the study center should make every effort to contact the subject (see Section 6.1) and reschedule the missed visit as soon as possible. The subject should be counseled on the importance of visit compliance and should be questioned as to whether he or she wishes to continue in the study.

7. Study Assessments and Procedures

7.1. Subject Entry Procedures

Subject informed consent must be obtained prior to conducting screening procedures. Each signature must be personally dated by each signatory and the original retained by the PI as part of the study record. A signed copy must be provided to each subject (refer to Section 4.3).

7.2. Schedule of Visits and Procedures

It is recommended that study visits be scheduled at approximately the same time of day throughout the trial. Subject assessments of GL, FHL, and LCL severity (ie, PFWS, PFHWS, and PLCWS) must be completed prior to investigator assessments (ie, IGA-FWS, IGA-FHLS, and IGA-LCWS). In addition, subjects should complete the PNA, P-GAIS, and Satisfaction with Treatment items prior to completing the FASE and FACE-Q assessments. The IGA-FHWS, IGA-FWS, IGA-LCWS, and Investigator GAIS should be performed by the same evaluator throughout the study. If it is not possible to use the same evaluator throughout the study, two evaluators should examine the subject together and discuss findings for at least 1 prior visit. The SOA is provided in Section 1.3.

7.2.1. Screening Visit

The Screening Visit must take place within 14 days prior to the treatment visit (Day 1 Visit).

The following procedures must be performed and recorded at this visit:

1. Review study procedures and information regarding the trial and obtain written informed consent and privacy authorization (as applicable).
2. Review eligibility criteria.
3. Obtain medical/surgical history, including prior toxin use, and demographic information, including Fitzpatrick skin phototype.

4. Conduct patient education: Discuss the potential effect of DAXI for injection treatment, explain the PFWS, PFHWS, and PLCWS measurements and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for GL, FHL, and LCL severity. Use the provided Patient Education Brochure.

9. Perform a physical examination.

11. Measure and record vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure); subjects should sit for 5 minutes prior to taking pulse and blood pressure.

13. Collect blood and urine samples for clinical safety laboratory tests (hematology, serum chemistry, PT, and urinalysis).

The Screening Visit clinical laboratory test results and UPT must be reviewed and signed by the investigator; any abnormal results must be determined to be not clinically significant by the investigator prior to enrollment.

7.2.2. Treatment Visit (Day 1)

The Treatment Visit (Day 1 Visit) must be performed within 14 days of the Screening Visit. The following procedures must be performed and recorded for each visit:

Prior to Investigational Product Administration

1. Confirm that all screening procedures have been completed, results reviewed, and recorded.
2. Review eligibility criteria.
3. Update medical/surgical history.

[redacted]

7. Conduct patient education. Discuss the potential effect of DAXI for injection treatment, explain the PFWS, PFHWS, and PLCWS measurements and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for GL, FHL, and LCL severity. Use the provided Patient Education Brochure.

[redacted]

15. Measure and record vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure). Subjects must sit for 5 minutes prior to having pulse and blood pressure measurements taken.

17. Update concomitant therapy/medications since screening, documenting the dose and dosing regimen of all prescription and non-prescription therapies and medications, including herbs, vitamins, or other nutritional supplements (Section 5.3).

Investigational Product Preparation

The assigned investigational product will be prepared by the trained dose preparer according to trial-specific instructions. The prepared investigational product will be provided in syringes to the investigator for administration.

Investigational Product Administration

Investigational product will be administered by the investigator to injection sites in the designated treatment areas

After Investigational Product Administration

obtain vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressures).

7.2.3. Week 1 Follow-Up Phone Call

At the Week 1 follow-up phone call, the subject will be contacted by the site staff for a health status check, concomitant therapy/medication check, and a query about AEs that may have occurred.

The following procedures must be performed and recorded:

1. Query subject about any new or ongoing AEs since the last visit

7.2.4. Follow-up Visits

At Weeks 2, 4, 8, 12, 16, 20, 24, 28, and 32, the following procedures must be performed and recorded:

2. Conduct patient education: discuss the potential effect of DAXI for injection treatment, explain the PFWS, PFHWS, and PLCWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for severity grading. Use the provided Patient Education Brochure.

14. Collect blood and urine samples for clinical safety laboratory tests (hematology, serum chemistry, and urinalysis) (Week 4 Visit only).

17. Assess any new or ongoing AEs since the last visit.

7.2.5. Final Evaluation Visit (Week 36) or Early Discontinuation

The following procedures must be performed and recorded at the Final Evaluation Visit for each subject. Following treatment, subjects will be followed until Week 36, or until the time when severity scores for GL, FHL, and LCL return to baseline (Day 1 pretreatment) or worse, based on both the investigator and subject evaluations (minimum of 24 weeks and up to 36 weeks after treatment), whichever occurs first. Subjects will then have a Final Evaluation Visit at which time the following procedures must be performed:

patient education: discuss the potential effect of DAXI for injection treatment, explain the PFWS, PFHWS, and PLCWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for severity grading. Use the provided Patient Education Brochure.

8. Perform a physical examination

[redacted]

14. Measure and record vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure).

[redacted]

16. Collect blood and urine samples for clinical safety laboratory tests (hematology, serum chemistry, and urinalysis).

[redacted]

If there are no safety concerns, the subject's participation in the study is complete at this visit.

7.2.6. Variation from Scheduled Visit Days

To allow for scheduling flexibility, limited variation will be permitted from the specified time of each visit (Table 4).

Table 4: Allowed Variation from Scheduled Visit Days

Visit	Allowed Variation
Week 1 Safety Call	+ 2 days
Week 2, Week 4	± 3 days
Weeks 8, 12, 16, 20, 24, 28, 32, and 36	±7 days

7.3. Efficacy Assessments

Investigator assessments should be performed by the same evaluator throughout the study for a given subject. It is recommended that visit assessments be completed as close to the same time of day as possible.

Subject assessments of GL, FHL, and LCL severity (ie, PFWS, PFHWS, and PLCWS) must be completed prior to investigator assessments (ie, IGA-FWS, IGA-FHLS, and IGA-LCWS). In addition, subjects should complete the PNA, P-GAIS, and Satisfaction with Treatment items prior to completing the FASE and FACE-Q assessments. Subjects who wear contact lenses should view the treatment areas while wearing their contact lenses. Subjects who wear glasses must have sufficient visual acuity to view the treatment areas without glasses. Subject assessments of GL, FHL, and LCL severity should be performed at rest first, followed by the assessment at maximum contraction.

The IGA-FWS, IGA-FHWS and IGA-LCWS will be conducted with the subject in a sitting position in a room with good overhead lighting or natural light from a window (but not direct sunlight). To ensure consistent eye positioning during the assessment, the investigator should ask the subject to focus on a fixed point in the examination room. Investigator assessments of GL,

FHL, and LCL severity should be performed at rest first, followed by the assessment at maximum contraction.

Planned timepoints for all efficacy assessments are provided in the SOA (Section 1.3).

7.3.1. Patient Frown Wrinkle Severity (PFWS)

Subjects will assess the visual appearance of GL using the PFWS at rest and at maximum frown. The assessment form will be provided directly to the subject to complete while reviewing their GL treated area using the supplied handheld mirror. The assessment will represent wrinkle severity at the given time point and will not be based on a comparison to the pre-treatment defect level. More detail is provided in Appendix 2.

Table 5: Patient Frown Wrinkle Severity (PFWS)

Rating Score	Frown Wrinkle Severity	Description
0	None	No wrinkles
1	Mild	Very shallow wrinkles
2	Moderate	Moderate wrinkles
3	Severe	Deep wrinkles

7.3.2. Patient Forehead Wrinkle Severity (PFHWS)

Subjects will assess the visual appearance of FHL using the PFHWS at rest and at maximum eyebrow elevation. The assessment form will be provided directly to the subject to complete while reviewing the FHL areas using the supplied handheld mirror. The assessment will represent wrinkle severity at the given time point and will not be based on a comparison to the pre-treatment defect level. More detail is provided in Appendix 3.

Table 6: Patient Forehead Wrinkle Severity (PFHWS)

Rating Score	Forehead Wrinkle Severity	Description	
		At Rest	At Maximum Eyebrow Elevation
0	None	No horizontal forehead lines	None to minimally visible horizontal forehead line(s)
1	Mild	Barely visible, shallow horizontal forehead line(s)	Visible, shallow horizontal forehead line(s)
2	Moderate	Clearly visible, moderate depth horizontal forehead line(s)	Clearly visible, moderate depth horizontal forehead line(s)
3	Severe	Clearly visible, deep horizontal forehead line(s) with redundancy of skin	Clearly visible, deep horizontal forehead line(s) with redundancy of skin

7.3.3. Patient Lateral Canthal Wrinkle Severity (PLCWS)

Subjects will assess the visual appearance of LCL using the PLCWS at rest and at maximum smile, to assess the severity of the LCL on each side of the face (a separate score will be assigned for each side). The assessment form will be provided directly to the subject to complete while reviewing his or her LCL using the supplied handheld mirror. The assessment will represent wrinkle severity at the given time point and will not be based on a comparison to the pre-

treatment defect level. Scores at screening and baseline must be consistent bilaterally. More detail is provided in Appendix 4.

Table 7: Patient Lateral Canthal Wrinkle Severity (PLCWS)

Rating Score	Lateral Canthal Wrinkle Severity	Description
0	None	No line(s) lateral to the lateral canthus
1	Mild	Barely visible, shallow line(s) lateral to the lateral canthus
2	Moderate	Clearly visible, moderately deep line(s) lateral to the lateral canthus
3	Severe	Clearly visible deep line(s) lateral to the lateral canthus with redundancy of skin

7.3.4. Global Aesthetic Improvement Scale (GAIS)

The investigator and subject will assess the visual appearance (at maximum contraction) of the improvement from the baseline condition in GL, FHL, and LCL (individually) using the following 7-point severity GAIS (Table 8). Subjects will use the baseline assessment photograph for comparison when reviewing the visual appearance for GL, FHL, and LCL to assess improvement following treatment.

The Patient GAIS assessment form (Appendix 5) will be provided directly to the subject to complete while reviewing each treatment area (at maximum contraction) using the supplied handheld mirror. These subject assessments must be completed before the investigator completes the IGA assessments and the investigator GAIS.

Table 8: Global Aesthetic Improvement Scale (GAIS)

Rating Score	Wrinkle Improvement
-3	Very Much Worse
-2	Much Worse
-1	Worse
0	No Change
1	Improved
2	Much Improved
3	Very Much Improved

7.3.5. Facial Age Self Evaluation (FASE)

Subject will be asked to rate their perceived age on a FASE questionnaire (Appendix 6). This assessment will be given after the subject's completion of the Patient GAIS, the subject will be given a questionnaire to rate their perception of how old they think they look following the treatment.

7.3.6. Subject Global Satisfaction with Treatment Questionnaires

Subject will provide a rating of their satisfaction with the treatment results. Following the subject's completion of the Patient GAIS, the subject will be given the Subject Global Satisfaction with Treatment Questionnaires to rate their satisfaction with the treatment results.

Subjects will be asked how satisfied or dissatisfied they are with how the treated area of the face looks (Appendix 7).

7.3.7. FACE-Q™

Subject will be asked to complete the FACE-Q™ Appraisal of Lines: Overall, FACE-Q™ Appraisal of Lines: Forehead, FACE-Q™ Appraisal of Lines: Between Eyebrows, FACE-Q™ Appraisal of Lines: Crow's Feet Lines, FACE-Q™ Satisfaction with Forehead and Eyebrows, FACE-Q™ Satisfaction with Outcome and FACE-Q™ Psychological Function. Refer to Appendix 8.

7.3.8. Patient Naturalness Assessment (PNA)

The subject will be asked to rate how strongly they agree or disagree with the statement "the results of my treatment look natural." More detail is provided in Appendix 9.

7.3.9. Investigator Global Assessment Frown Wrinkle Severity (IGA-FWS)

The investigator will assess the visual appearance of the GL at rest first, and then at maximum frown using the IGA-FWS with the following 4-point scale (Table 9). More detail is provided in Appendix 10.

Table 9: Investigator Global Assessment Facial Wrinkle Severity (IGA-FWS)

Rating Score	Frown Wrinkle Severity	Description
0	None	No wrinkles
1	Mild	Very shallow wrinkles
2	Moderate	Moderate wrinkles
3	Severe	Deep and furrowed wrinkles

The assessment will represent wrinkle severity at the given time point and will not be based on a comparison to the pre-treatment level. Assessments should be completed by the same Revance-approved and trained investigator and conducted as close to the same time of day as possible at each visit. To ensure standardized ratings of wrinkle severity across investigators, a set of training photographs exhibiting the grades of wrinkle severity will be used for training. A photo guide will be provided to each study center to assist in the investigator's assessment.

7.3.10. Investigator Global Assessment Forehead Wrinkle Severity (IGA-FHWS)

The investigator will assess the visual appearance of the FHL at rest first and then at maximum eyebrow elevation using the IGA-FHWS with the following 4-point scale (Table 10). More detail is provided in Appendix 11.

Table 10: Investigator Global Assessment Forehead Wrinkle Severity (IGA-FHWS)

Rating Score	Forehead Wrinkle Severity	Description	
		At Rest	At Maximum Eyebrow Elevation
0	None	No horizontal forehead lines	None to minimally visible horizontal forehead line(s)
1	Mild	Barely visible, shallow horizontal forehead line(s)	Visible, shallow horizontal forehead line(s)
2	Moderate	Clearly visible, moderate depth horizontal forehead line(s)	Clearly visible, moderate depth horizontal forehead line(s)
3	Severe	Clearly visible, deep horizontal forehead line(s) with redundancy of skin	Clearly visible, deep horizontal forehead line(s) with redundancy of skin

[redacted]

7.3.11. Investigator Global Assessment of Lateral Canthal Wrinkle Severity (IGA-LCWS)

The investigator will assess the visual appearance of the LCL on each side of the face, at rest first and then at maximum smile, using the IGA-LCWS with the following 4-point scale (Table 9). More detail is provided in (Appendix 12).

Table 11: Investigator Global Assessment Lateral Canthal Wrinkle Severity (IGA-LCWS)

Rating Score	Lateral Canthal Wrinkle Severity	Description
0	None	None to minimally visible line(s) lateral to the lateral canthus
1	Mild	Visible, shallow line(s) lateral to the lateral canthus
2	Moderate	Clearly visible, moderately deep line(s) lateral to the lateral canthus
3	Severe	Clearly visible, deep line(s) lateral to the lateral canthus with redundancy of skin

The assessment will represent wrinkle severity at the given time point and will not be based on a comparison to the pre-treatment level. Assessments should be completed by the same Revance-approved and trained investigator and conducted as close to the same time of day as possible at each visit. To ensure standardized ratings of wrinkle severity across investigators, a

set of training photographs exhibiting the grades of wrinkle severity will be used for investigator training. A photo guide will be provided to each study center to assist in the investigator's assessment. Scores at screening and baseline must be consistent bilaterally.

[redacted]

7.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the SOA (Section 1.3).

7.4.1. Adverse Events and Serious Adverse Events

7.4.1.1. Evaluation of Adverse Events and Serious Adverse Events

For this protocol, an **adverse event (AE)** is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, clinically significant abnormal laboratory finding, injury or accident) that emerges or worsens following administration of investigational product and until the end of study participation that may not necessarily have a causal relationship to the administration of the investigational product. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory result), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. A treatment-emergent AE is one that occurs after any period of exposure to treatment.

Pre-existing conditions, which increase in frequency or severity or a change in nature as a consequence of an investigational product use will also be considered an adverse event.

An unexpected AE is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Any change in the study safety evaluations, (e.g., vital signs, injection site evaluation) post-treatment determined to be clinically significant by the investigator must be reported as an AE.

An **SAE** is any untoward medical occurrence that results in any of the following outcomes:

- Death

- Life-threatening, (i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred. It does not apply to an AE that hypothetically might have caused death if it were more severe)
- Persistent or significant disability/incapacity or substantial disruption of the subject's ability to carry out normal life functions
- Requires in-patient hospitalization or prolongs hospitalization (i.e., a prolonged hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)
- Congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the molecule or investigational product before conception or during pregnancy)
- Does not meet any of the above serious criteria but based upon appropriate medical judgement may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above (i.e., is a significant or important medical event)

7.4.1.2. Assessment and Reporting Requirements

The investigator will assess each subject post-treatment and at each subsequent study visit for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following non-leading question: "How have you felt since your last visit?" All AEs (serious and non-serious) will be collected from the signing of the ICF until the Final Evaluation Visit. Any AE reported by the subject must be recorded on the source documents and eCRFs.

All AEs will be collected after IP administration until Week 36 or the Final Evaluation Visit at all timepoints as specified in the SOA (Section 1.3). Medical occurrences related to protocol-mandated intervention that begin before the start of study intervention but after obtaining informed consent will be recorded as AEs.

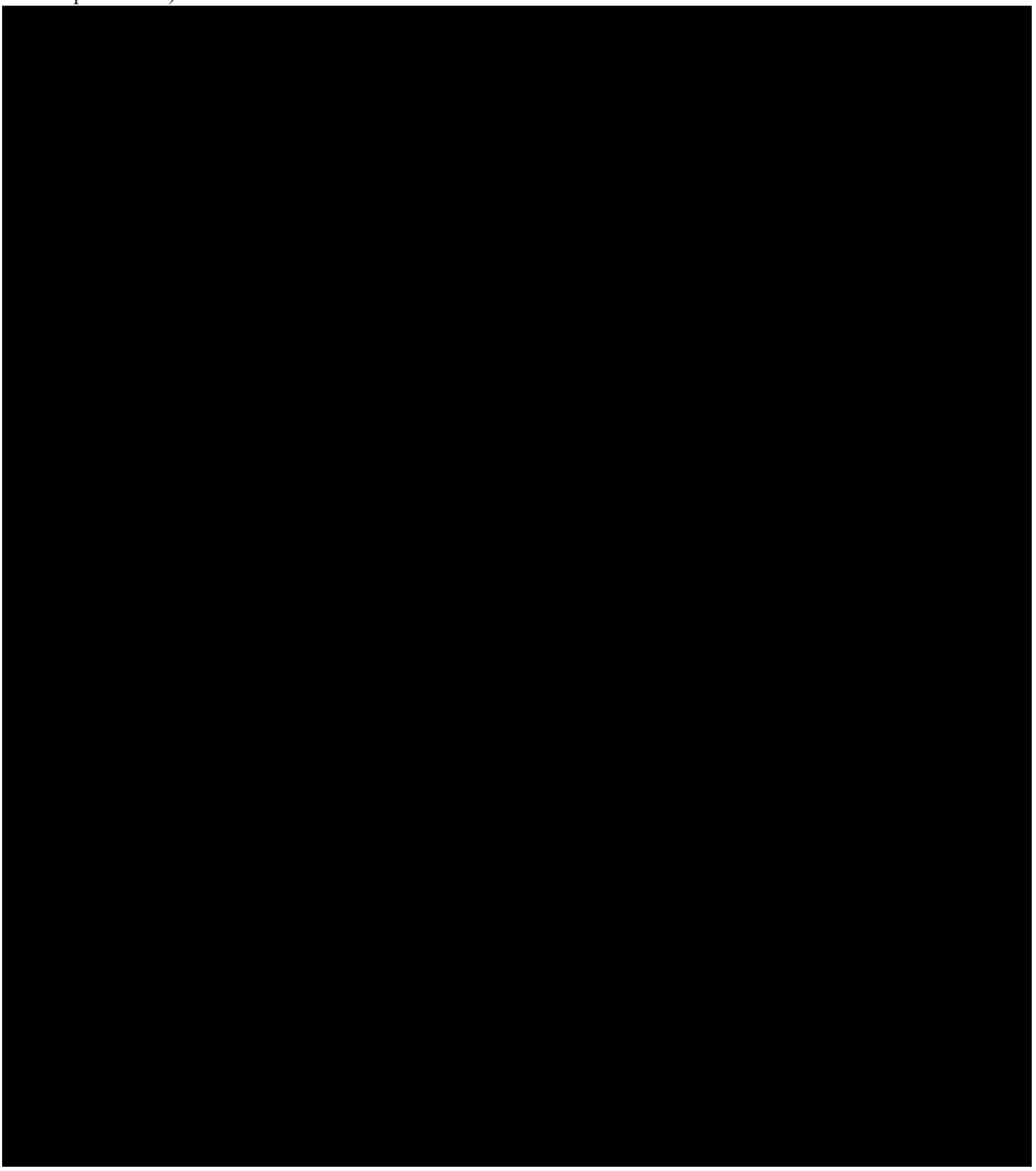
All SAEs will be recorded and reported to Revance or designee immediately within 24 hours of their awareness of the event. All fatal or life-threatening SAEs should be telephoned to Revance or the designee's authorized representative as soon as the investigator learns of the event.

7.4.1.3. Serious Adverse Events

The investigator must report an SAE to Revance or the designee's authorized representative within 24 hours of their awareness of the event:

1. Complete and return an SAE Form with all information known to date; including the investigator's assessment of causality
2. Contact Revance or the authorized representative for a fatal or life-threatening event as soon as the investigator or study staff are aware of the event
3. Obtain and maintain all pertinent medical records (e.g., discharge summary, autopsy report) and medical judgments of medical personnel who assisted in subject's treatment and follow-up
4. Provide follow-up information to Revance or designee within 24 hours of awareness

Regulatory Authorities, IRBs/ IECs, and investigators will be notified of SAEs in accordance with applicable regulations and requirements (e.g., ICH-GCP, national regulations and local requirements).



[redacted]

7.4.1.5. Follow-up of Non-Serious Adverse Events

All AEs that are identified during the last scheduled study visit (or the Final Evaluation Visit, if applicable) must be recorded on the AE eCRF as ongoing.

Any clinically significant abnormal test results, (e.g., laboratory findings), at the final assessment should be followed to resolution or until determined by the investigator to be stabilized. Repeat tests may be indicated to establish this.

If a subject has any clinically significant, study-related abnormalities at the end of the study, the Medical Monitor should be notified and every effort made by the investigator to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities unless the Medical Monitor determines that follow-up is sufficient.

7.4.1.6. Follow-up of Post-Study Serious Adverse Events

Any SAEs that are identified on the last scheduled contact (or at early discontinuation, if applicable) must be recorded on the AE eCRF and reported to Revance or designee according to the reporting procedures outlined in Section 7.4.1.2. This may include unresolved previously reported SAEs or new SAEs. The investigator should follow these SAEs until the events are resolved, or the subject is lost-to-follow-up. The investigator should continue to report any significant follow-up information to the Medical Monitor, Revance or designee and the IRB/IEC up to the point the event has been resolved. Resolution means the subject has returned to the baseline state of health, or the Investigator does not expect any further improvement or worsening of the subject's condition.

Any new SAEs reported by the subject to the investigator that occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the administration of investigational product should be reported to Revance or designee and the IRB/IEC.

7.4.1.7. Investigational Product Causality and Severity

Relationship of an AE to investigational product will be assessed as follows:

- **Definite:** There is a clinically plausible time sequence between the onset of the AE and the administration of investigational product; when the event responds to withdrawal of investigational product and/or recurs with re-administration of investigational product
- **Probable:** There is a clinically plausible time sequence between the onset of the AE and the administration of investigational product; the AE is unlikely to be caused by the concurrent/underlying illness, other drugs or procedures

- **Possible:** There may or may not be a clinically plausible time sequence between the onset of the AE and the administration of investigational product and a cause cannot be ruled out
- **Unrelated:** There is not a temporal or causal relationship to investigational product administration

The investigator is responsible for evaluating all AEs and determining the severity of the event. Severity will be categorized as mild, moderate or severe according to the following definitions:

- **Mild:** Event may be noticeable to subject; does not influence daily activities; usually does not require intervention
- **Moderate:** Event may be of sufficient severity to make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed
- **Severe:** Event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually needed

7.4.2. Physical Examination

A targeted physical examination[redacted] will be conducted. Significant physical examination findings that are present prior to investigational product administration are to be included on the Medical History eCRF.

Significant physical examination findings after investigational product administration, which meet the definition of an AE, will be recorded on the AE eCRF post-treatment.

7.4.3. Vital Signs

Vital signs (i.e., body temperature, respiration rate, sitting radial pulse rate, and sitting systolic and diastolic blood pressures) will be obtained. Subjects must sit for 5 minutes prior to having pulse and blood pressure measurements taken. Any new abnormal findings or worsening from baseline at subsequent assessments, if judged clinically significant, should be recorded as an AE on the AE eCRF page.

[redacted]

7.4.4. Pregnancy Testing

A UPT is required for all WOCBP at screening, baseline (pre-treatment) and Week 36 or Final Evaluation Visit. A positive result prior to treatment will exclude the subject from study participation. The results of the UPT will be evaluated at each study center. If any subject has a positive UPT after treatment, a serum pregnancy test is required for confirmation.

If a female subject becomes pregnant while participating in the study, the investigator or site designee must complete the Pregnancy Report Notification Form provided by Revance or designee as soon as the pregnancy is confirmed (Section 4.6).

7.4.5. Injection Site Evaluation

Injection sites will be evaluated at screening to assess for skin inflammation or active skin disease and at later timepoints to determine if there is an immediate reaction to the investigational product. The assessment will be done as a global evaluation of the 5 GL injection sites, the 4 FHL injection sites, and each of the 3 injection sites for LCL on each side of the face. Refer to Appendix 13.

Table 12 Injection Site Evaluation

Assessment Descriptor	Present?	
	Yes	No
Erythema		
Edema		
Burning or Stinging (sensation as described by subject)		
Itching (sensation as described by subject)		
Bruising		

If the subject answers yes to any of these items, it should be captured and recorded as an AE.

7.4.6. Clinical Safety Laboratory Assessments

Table 13 outlines the clinical laboratory tests that will be conducted during this study. Blood and urine specimens will be collected using applicable safety precautions and will be processed according to the central clinical laboratory's instructions. Urinalysis will be evaluated at the study center using supplies provided by Revance or designee.

Table 13: Clinical Laboratory Tests

Serum Chemistry	Hematology	Urinalysis	Additional Tests
Glucose Total bilirubin Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Blood urea nitrogen	Hemoglobin Hematocrit Leukocyte Count (total) Leukocyte Count (differential) Red Blood Cell Count Platelet Count	Specific gravity pH Glucose Protein Blood Bilirubin Ketones	Prothrombin time (PT) (screening only) UPT (WOCBP only)*

*If positive at timepoints after study treatment, confirm by serum pregnancy test

It is the investigator's responsibility to review the results of all laboratory tests as they become available. For each laboratory test result outside the reference range, the investigator must ascertain if the abnormal lab result is a clinically significant result for that individual subject. Likewise, if laboratory tests are taken at follow-up visits, the investigator must ascertain if this is an abnormal and clinically significant change from pretreatment for that individual subject. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test.

The investigator must sign and date all written laboratory results (e.g., urinalysis, hematology, chemistry, PT, and pregnancy tests) and note Not Clinically Significant or Clinically Significant

for each out of range laboratory value. If a laboratory value is determined to be a clinically significant result for that subject, this will be considered an AE.

[redacted]

8. Statistical Considerations

8.1. Sample Size Determination

A sample size of 48 is selected [redacted]

8.2. Populations for Analyses

For purposes of analysis, the following populations are defined.

Population	Description
Enrolled	All subjects who signed ICF, confirmed eligible and received treatment
Evaluable	All enrolled subjects who receive treatment and have any post treatment assessment of IGA-FWS at maximum frown
Safety	All enrolled subjects who receive at least 1 treatment (injection)

8.3. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the detailed methods of analysis, the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the efficacy and safety endpoints.

8.3.1. Efficacy Analyses

In general, descriptive summaries will include means, standard deviations, median, lower and upper quartiles, and ranges for continuous variables; and counts and proportions for categorical measures. Kaplan-Meier curves will be plotted for each time-to-event endpoint and median duration with associated 95% CIs will be provided. Proportion of subjects with response at a given time point will be reported based on observed cases, as well as based on proportion of treated subjects. As this is an open-label study with no placebo comparator arm, no formal hypothesis tests are planned.

8.3.2. Safety Analyses

Adverse events (AEs) occurring during the study will be recorded and classified according to MedDRA terminology. Those occurred one or after treatment are considered as treatment emergent. All reported TEAEs will be summarized, in terms of the number of subjects reporting events, system organ class, preferred term, severity, relationship to study drug, outcome, action taken and seriousness. For summarization of event causality and seriousness, subjects will be counted only once within a system organ class or preferred term using the event with the event with the greatest relationship for causality and the event with the highest severity. A summary of TEAEs leading to discontinuation will also be provided.

A by-subject listing of any SAEs will be provided and all SAEs will be summarized by severity and relationship to study treatment.

Clinical laboratory test and vital sign results will be summarized by visit and if applicable a shift table will be used to evaluate the shift in status from baseline at each visit. Physical examination, injection site findings, will be summarized as described in the SAP.

8.4. Interim Analyses

A formal interim analysis of the data will be performed. Further details can be found in the SAP.

8.5. Missing Data

Missing data will be imputed with the worse value form the previous timepoint and the next timepoint, up to this subject's last visit. Details will be provided in the SAP.

9. Records Management

9.1. Data Collection

For this study, all protocol-specified data will be recorded in the source documents, and data will be entered on the eCRFs from the source documents. Upon each subject's completion of the study, the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents.

It is Revance's policy that the study data be verifiable with the source data that necessitates access to all original recordings, laboratory reports, and other records for each subject. The investigator must, therefore, agree to allow access to subjects' records, and source data must be made available for all study data. Subjects (or their legal representatives) must also allow access to their medical records. Subjects will be informed of the importance of increased record access and permission granted by signature on the ICF prior to any screening procedures.

Checks will be performed to ensure the quality, consistency, and completeness of the data. Instances of missing or un-interpretable data will be resolved with the investigator or Study Coordinator. Site personnel will be responsible for providing resolutions to data queries and for correcting the eCRFs, as appropriate. Any amendments and corrections necessary will be undertaken in both the source documents and eCRFs (as appropriate) and countersigned by the investigator, or documented designee, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids. All unused Revance or designee study materials and binders must be returned to Revance or designee upon completion of the study.

The investigator must keep written or electronic source documents for every subject participating in the clinical study. The subject file that identifies the study in which the subject is participating must include the subject's available demographic and medical information including:

- Name
- Contact information
- Date of birth
- Sex
- Medical history
- Concomitant diseases
- Concomitant therapies/medication
- Study visit dates
- Performed examinations, evaluations, and clinical findings
- Investigational product administration
- AEs, SAEs, or pregnancy (as applicable)

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment must be included in the subject's source document (e.g., laboratory value listings).

Subjects will authorize the use of their protected health information (PHI) during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose PHI will not be eligible to participate in the study. The investigator will ensure that the study documents forwarded to Revance or their designee, and any other documents, contain no subject names or other PHI, such as medical record number or date of birth.

Regulatory authorities, the IRB/IEC and/or Revance's Quality Assurance department (or designee) may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. The investigator must guarantee direct access to these documents. At the conclusion of the trial, Revance or designee will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in this protocol.

9.2. File Management at the Study Center

It is the responsibility of the investigator to ensure that the study center maintains all source and essential documents in accordance with ICH Guidance for Industry E6 (R2) Good Clinical Practice: Consolidated Guidance, Section 8 – Essential Documents for the Conduct of a Clinical Study.

9.3. Records Retention at the Study Center

It is a Revance requirement that all investigators participating in clinical studies maintain detailed clinical data for one of the following periods:

- Country-specific requirements, or
- A period of at least 2 years following the last approval of a marketing application approved by a Regulatory Authority in an ICH region or until there are no pending or contemplated marketing applications in an ICH region, or,
- A period of 2 years after Revance notifies the investigator that the data will not be submitted for review by any Regulatory Authority

Regardless of applicable retention period, the investigator must not dispose of any records or essential documents relevant to this study without either (1) written permission from Revance, or (2) providing an opportunity for Revance to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by Revance or designee and relevant regulatory agencies. If the investigator withdraws from the study (e.g., relocation, retirement) all study-related records should be transferred to a mutually agreed upon designee. Notice of such transfer will be provided to Revance in writing.

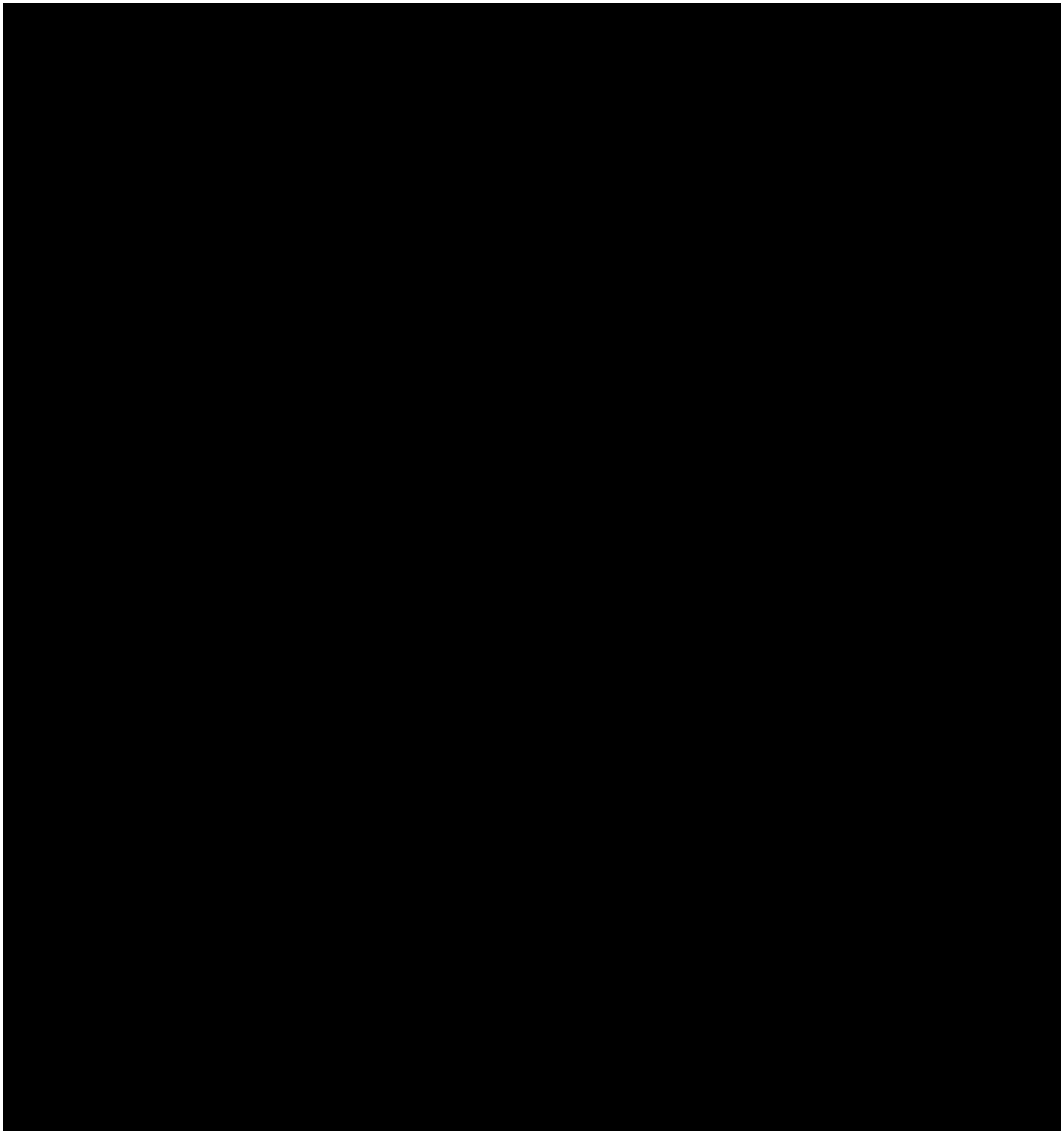
[redacted]

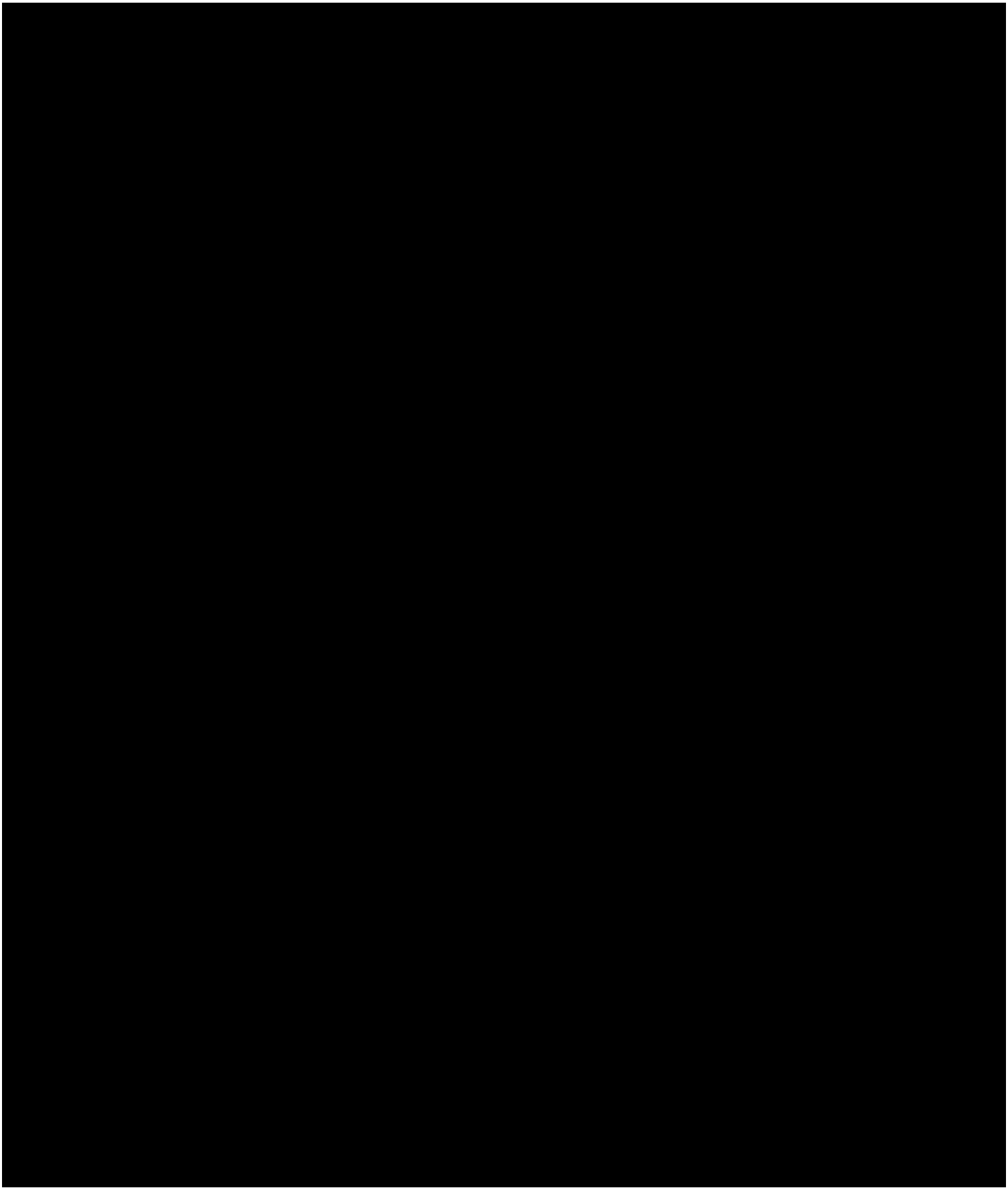
11. Ethics and Responsibility

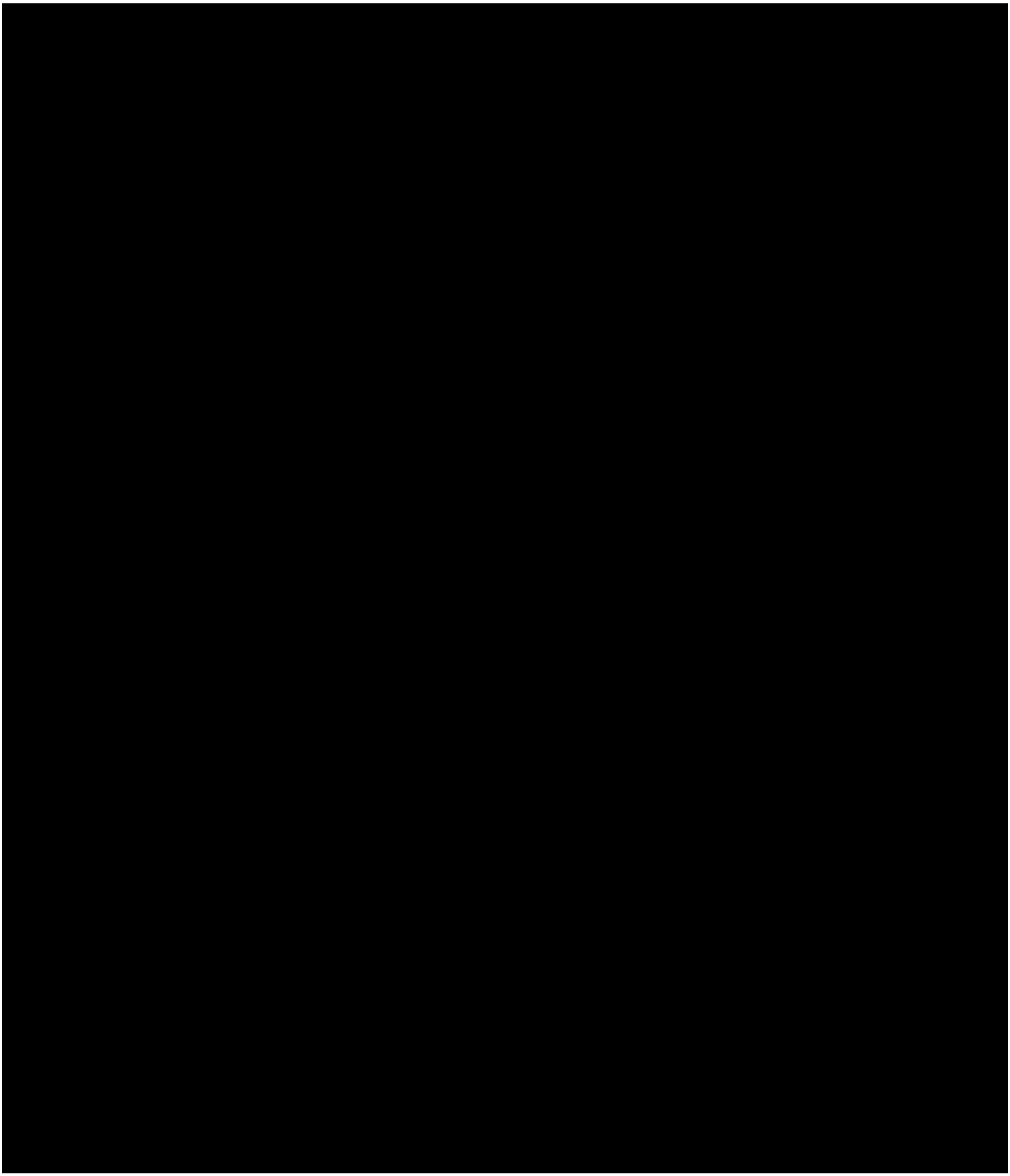
This study must be conducted in compliance with the protocol, the ICH Guidance for Industry E6 (R2) Good Clinical Practice: Consolidated Guidance and the applicable regulatory requirements. Investigators must submit all essential regulatory documentation, as required by local and national regulations (including IRB/IEC approval of the protocol and ICF) to Revance or designee before investigational product will be shipped to the study center.

[redacted]

[redacted]

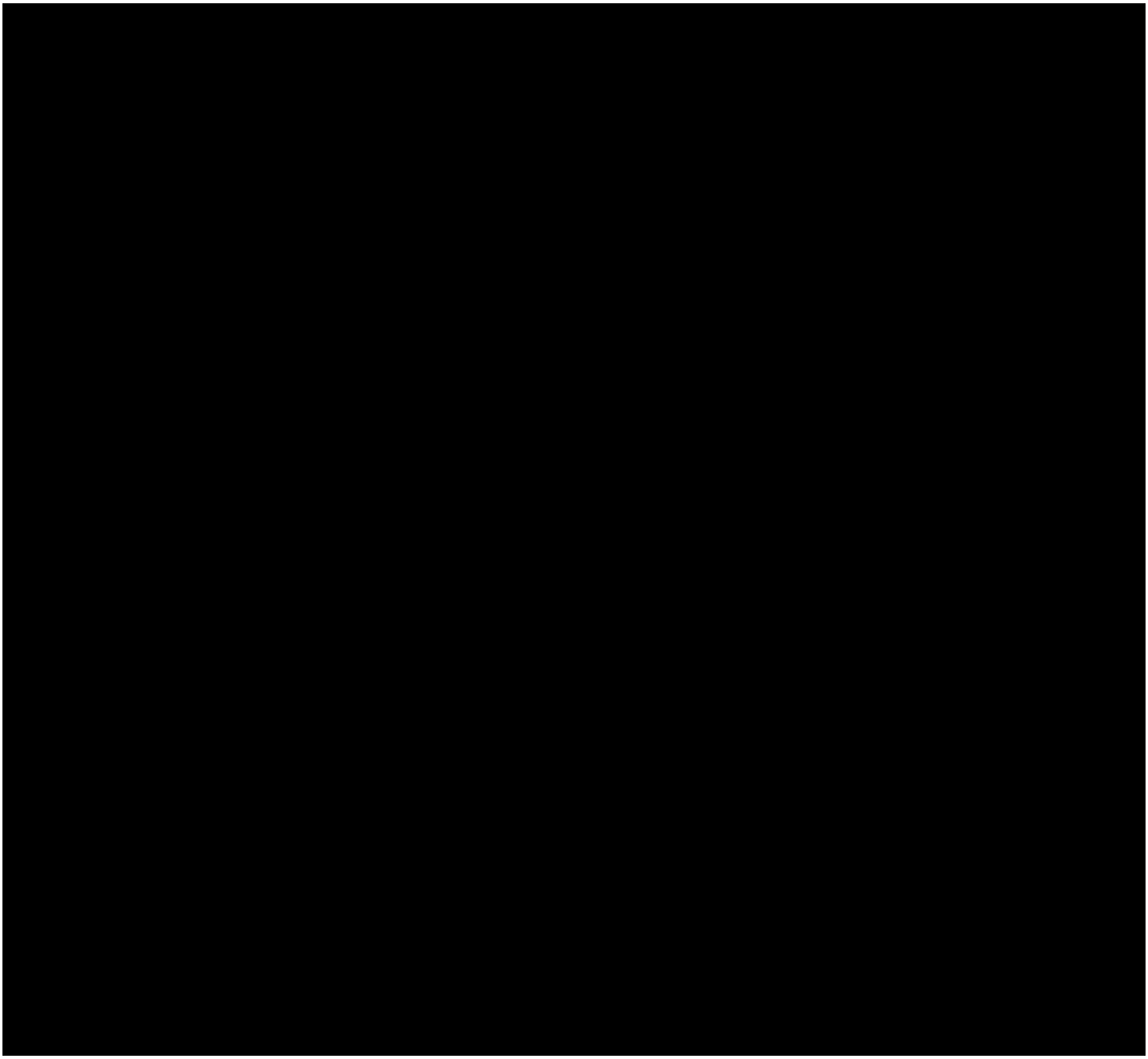






[redacted]

[redacted]

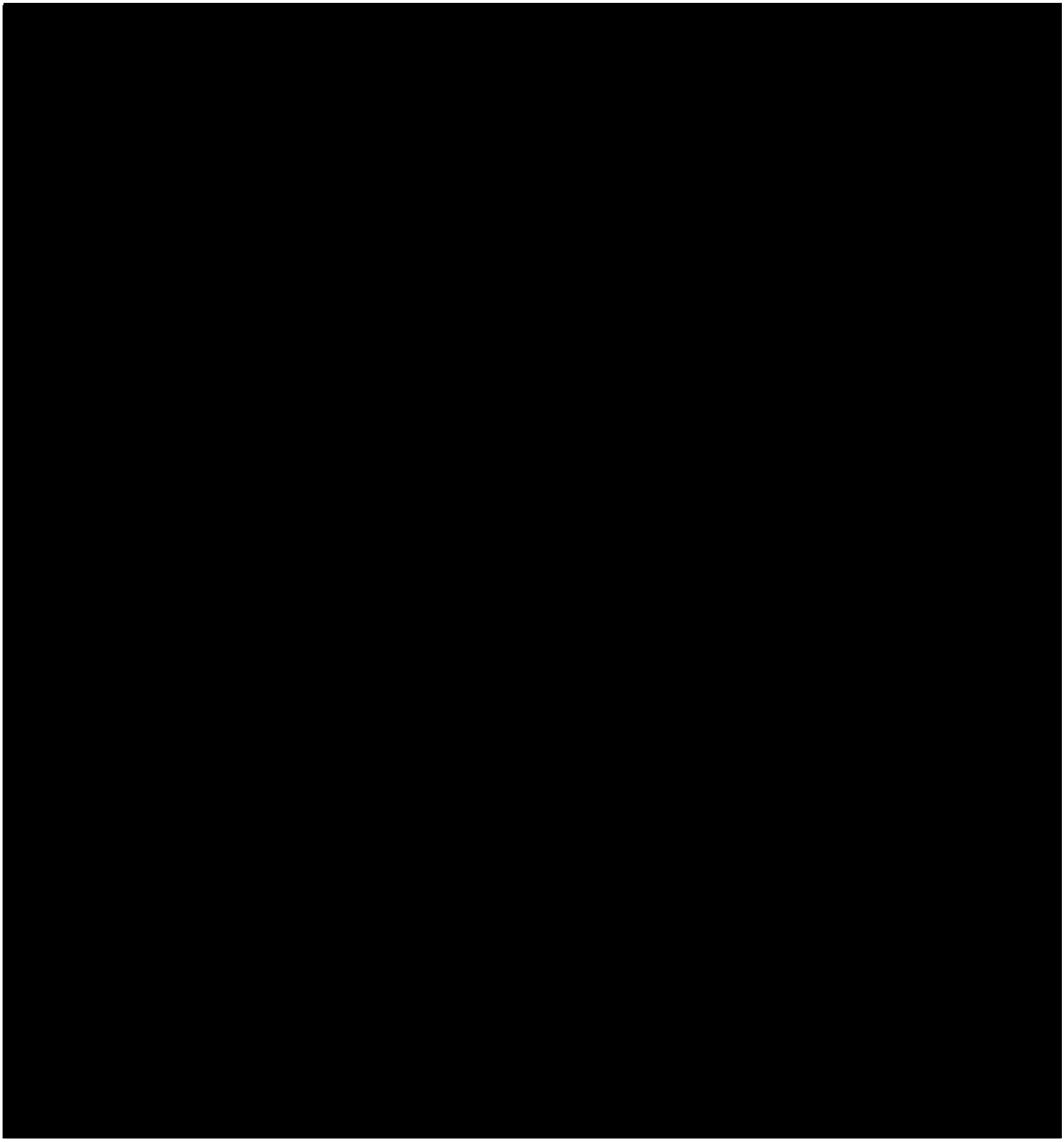


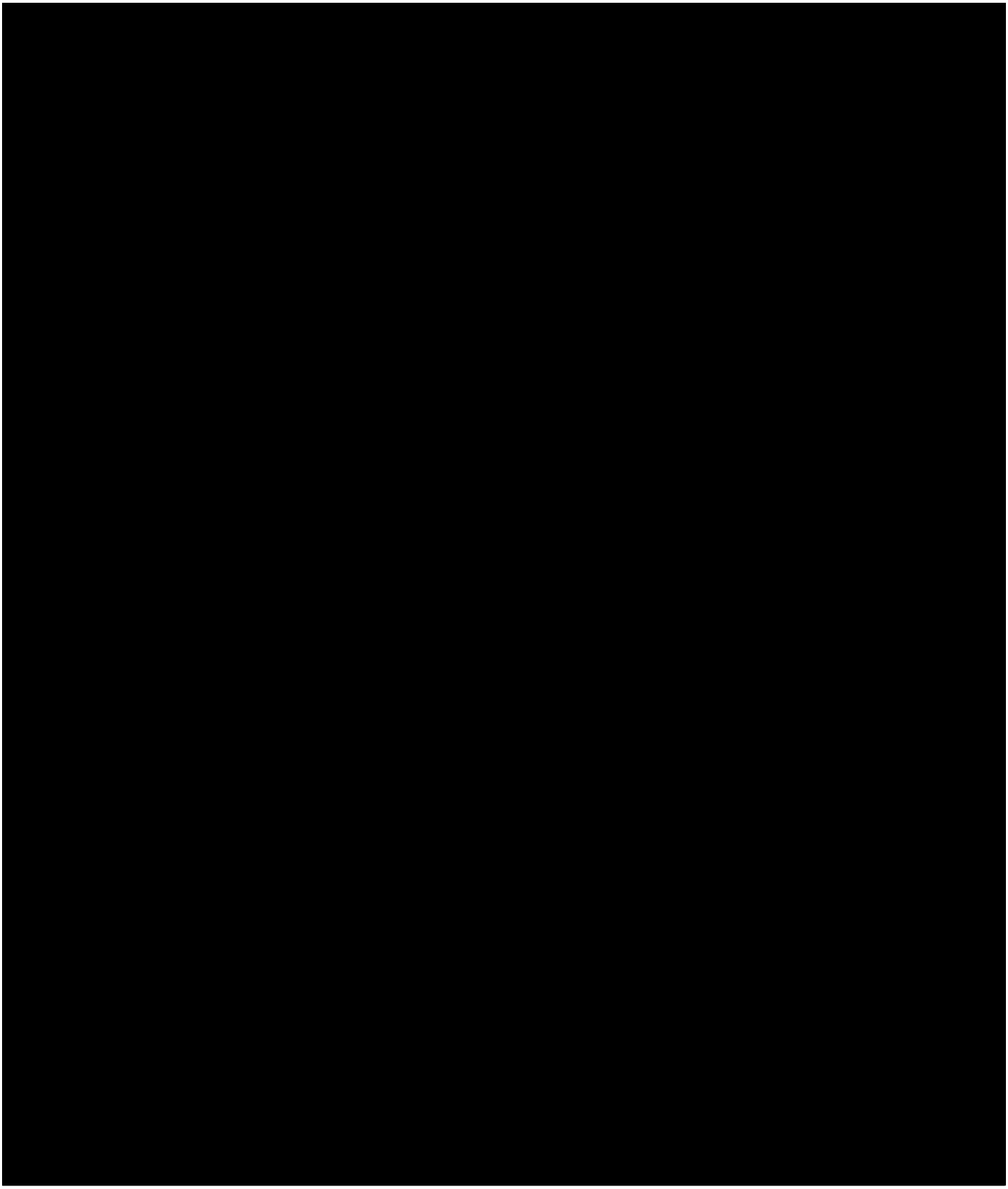
[redacted]

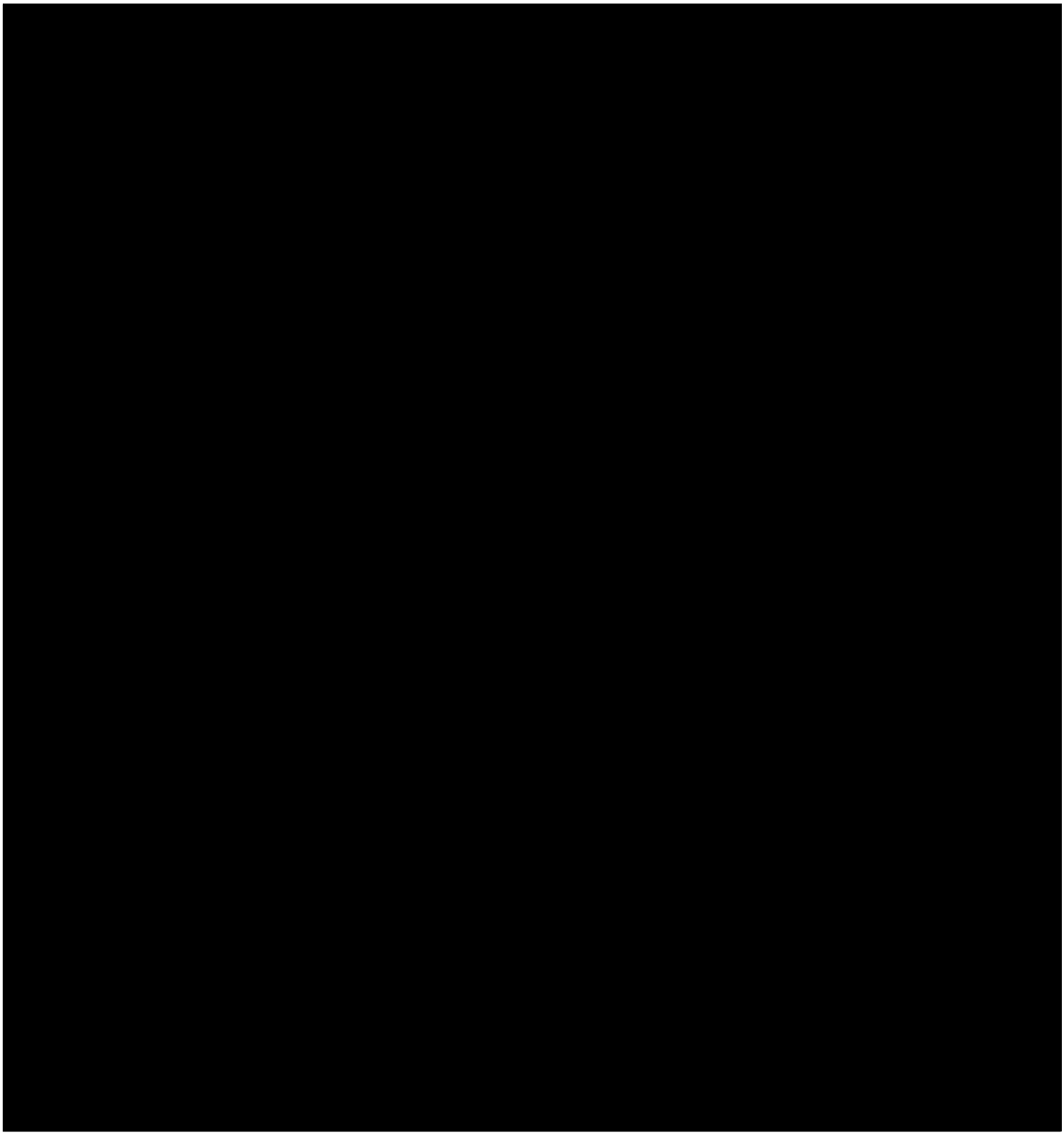
[redacted]

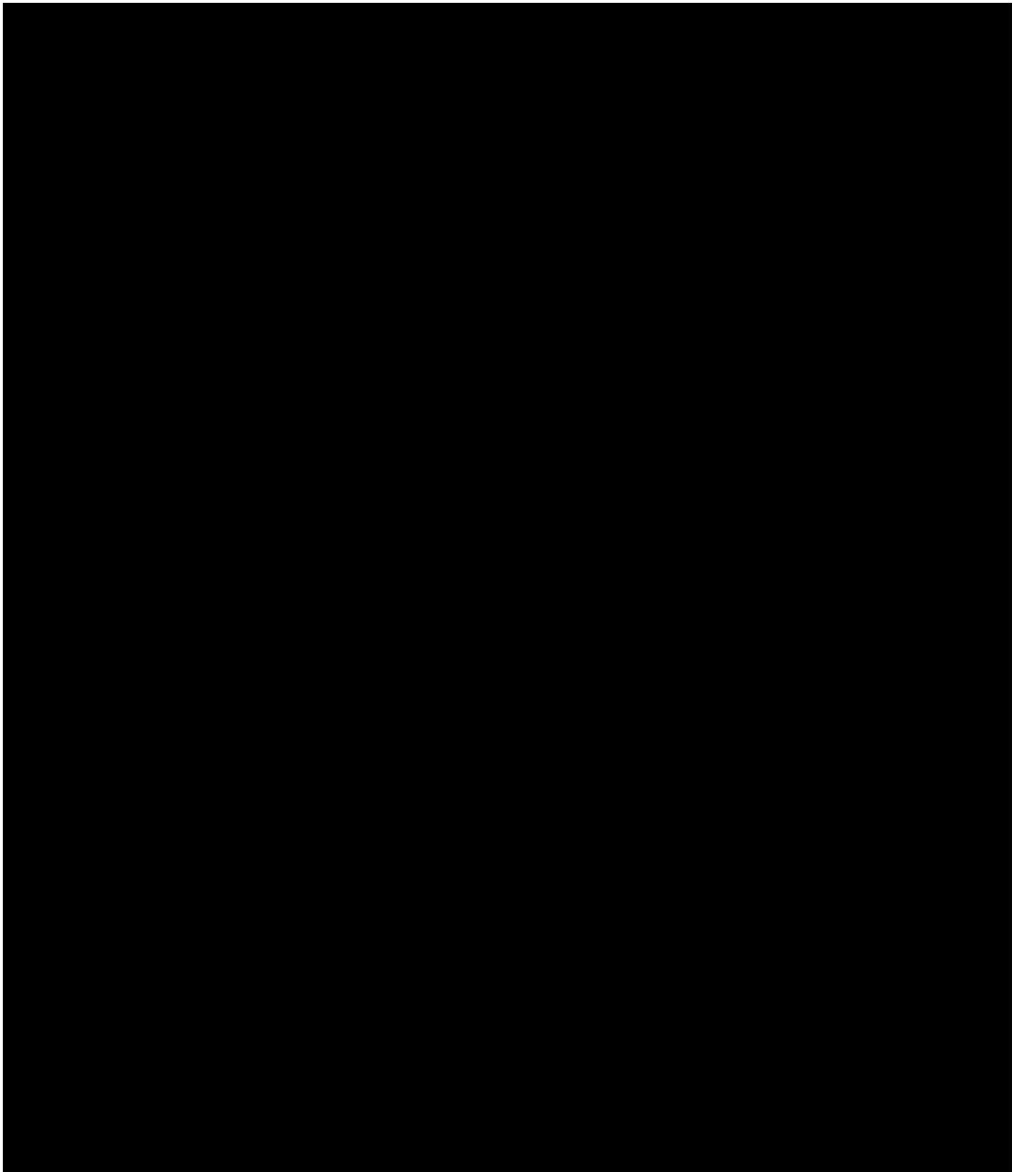
[redacted]

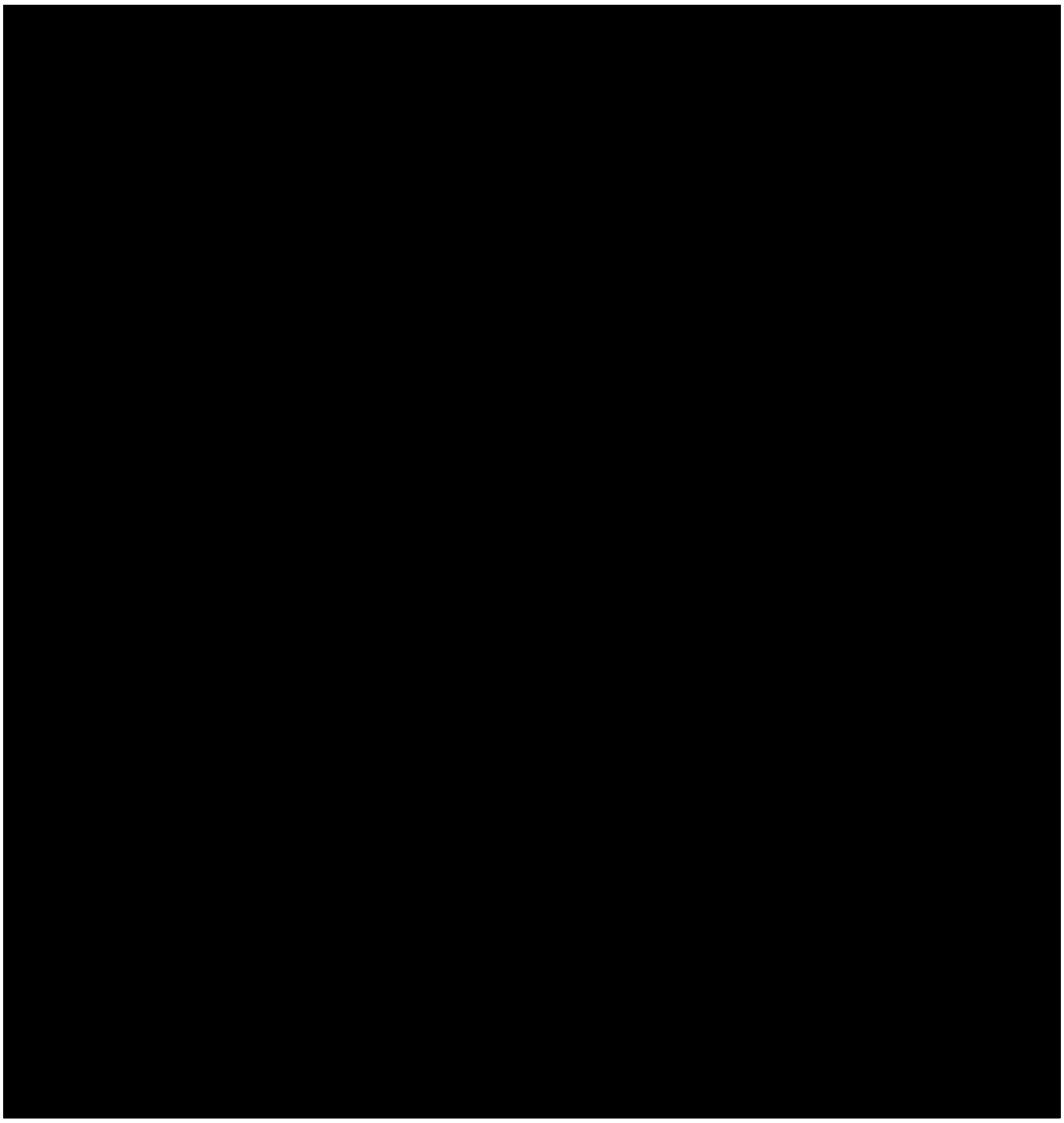
[redacted]

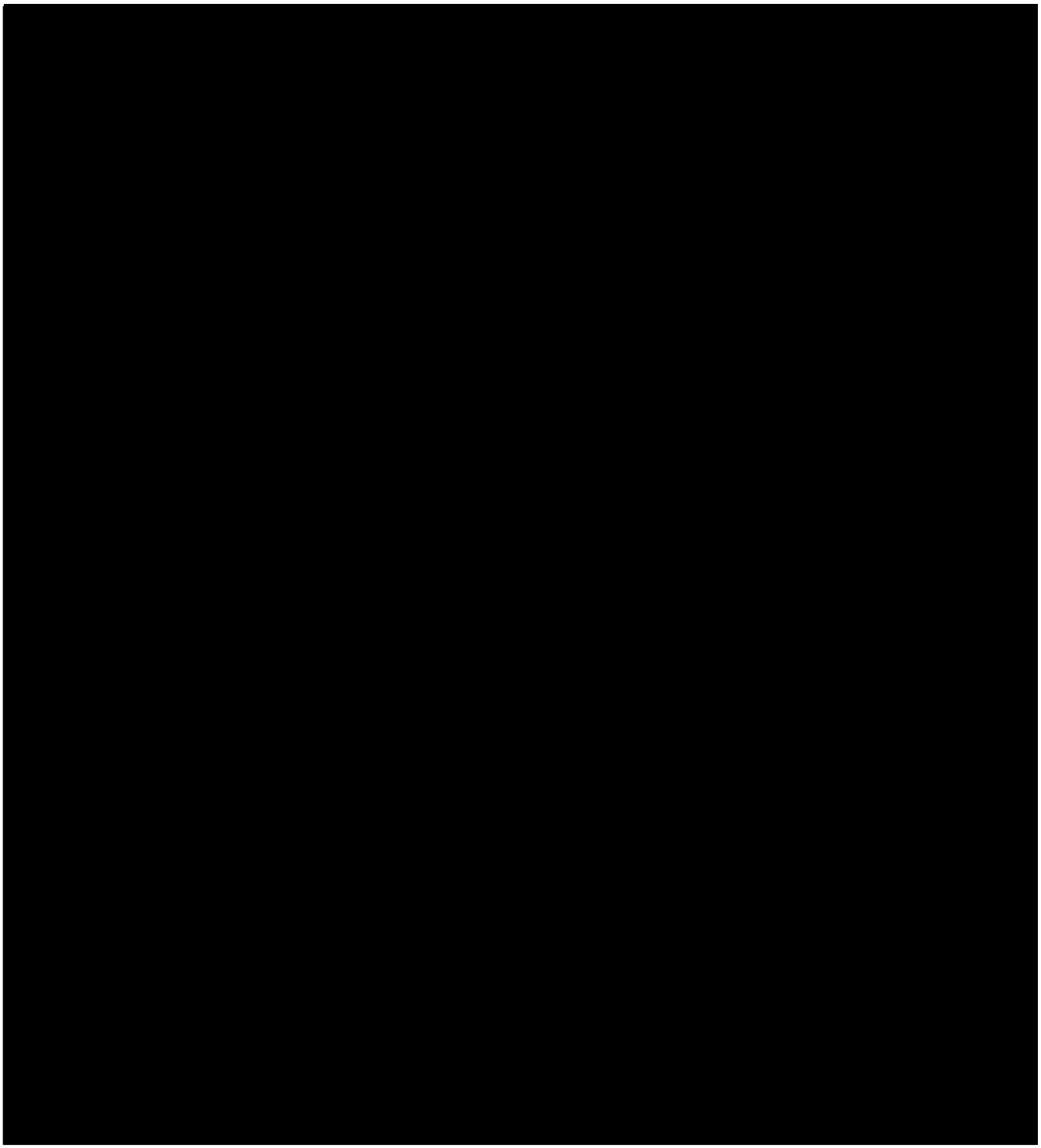




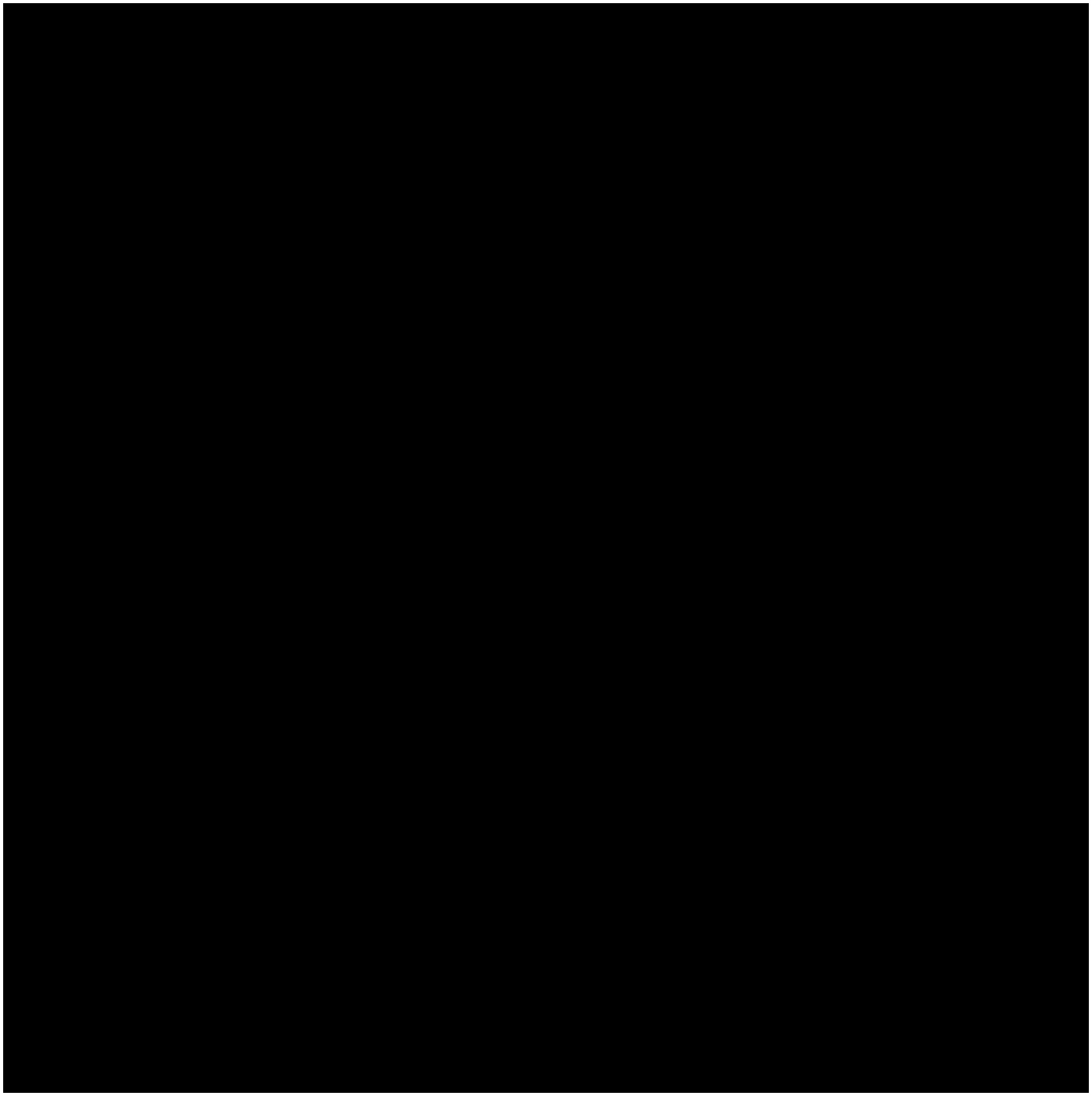




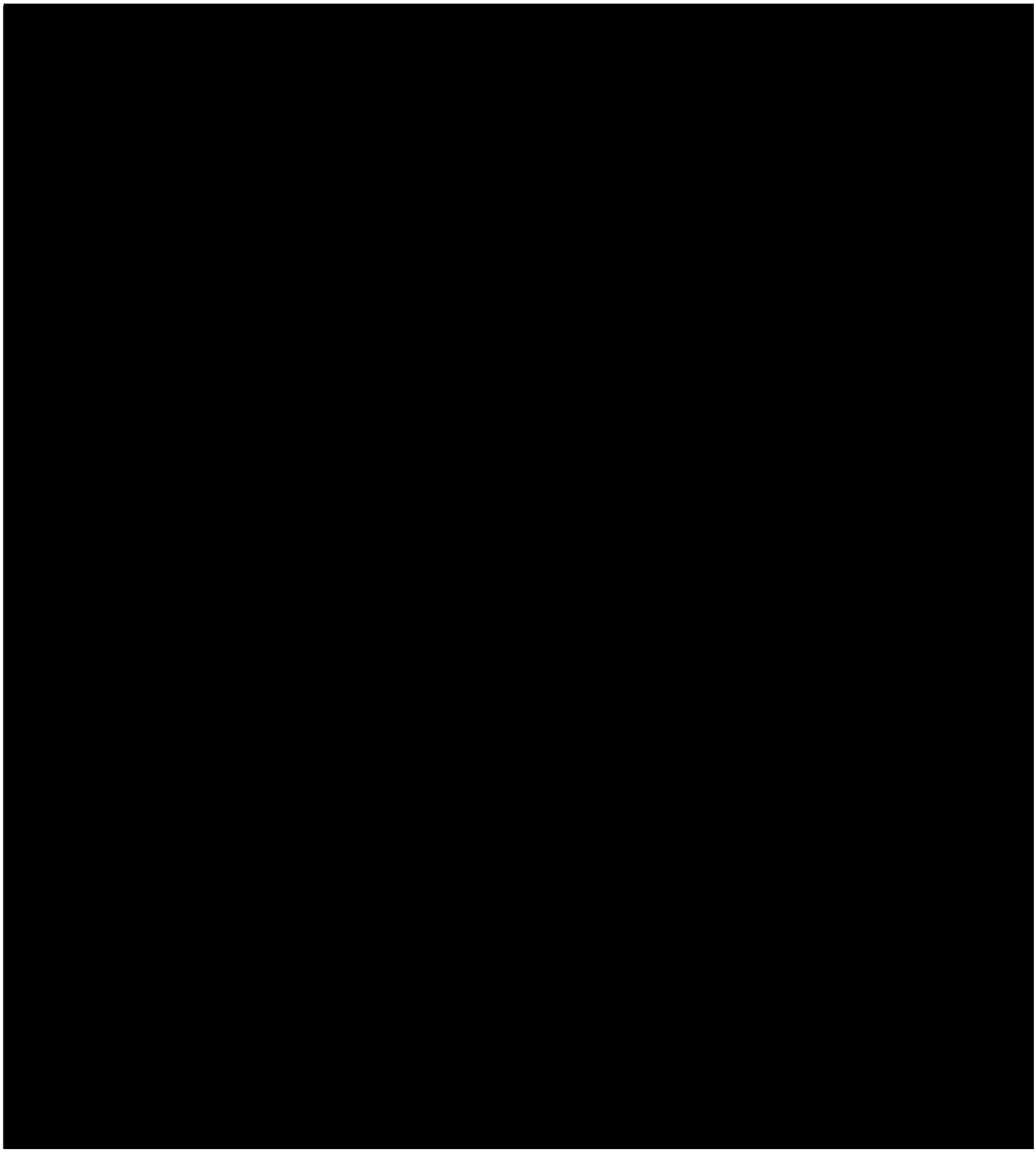


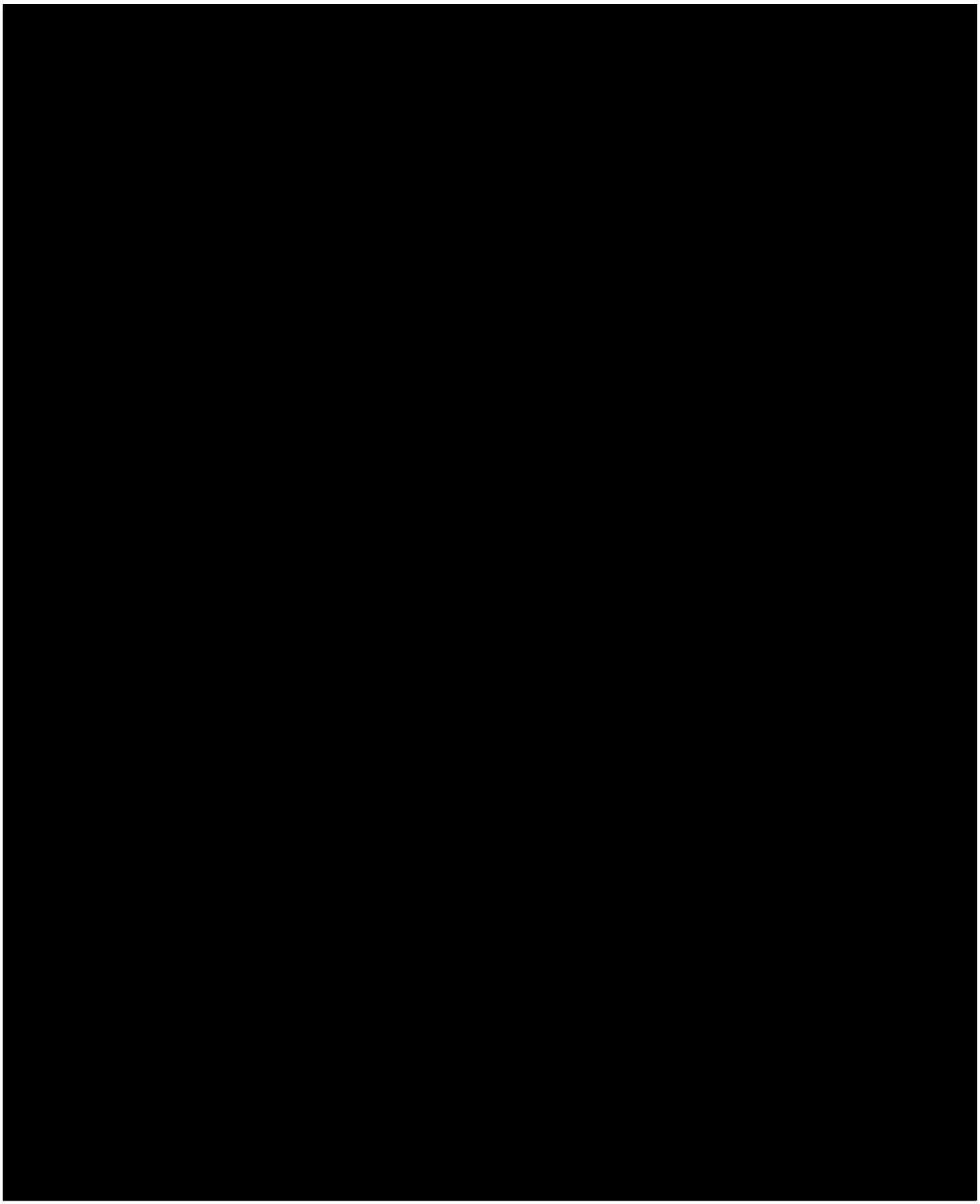


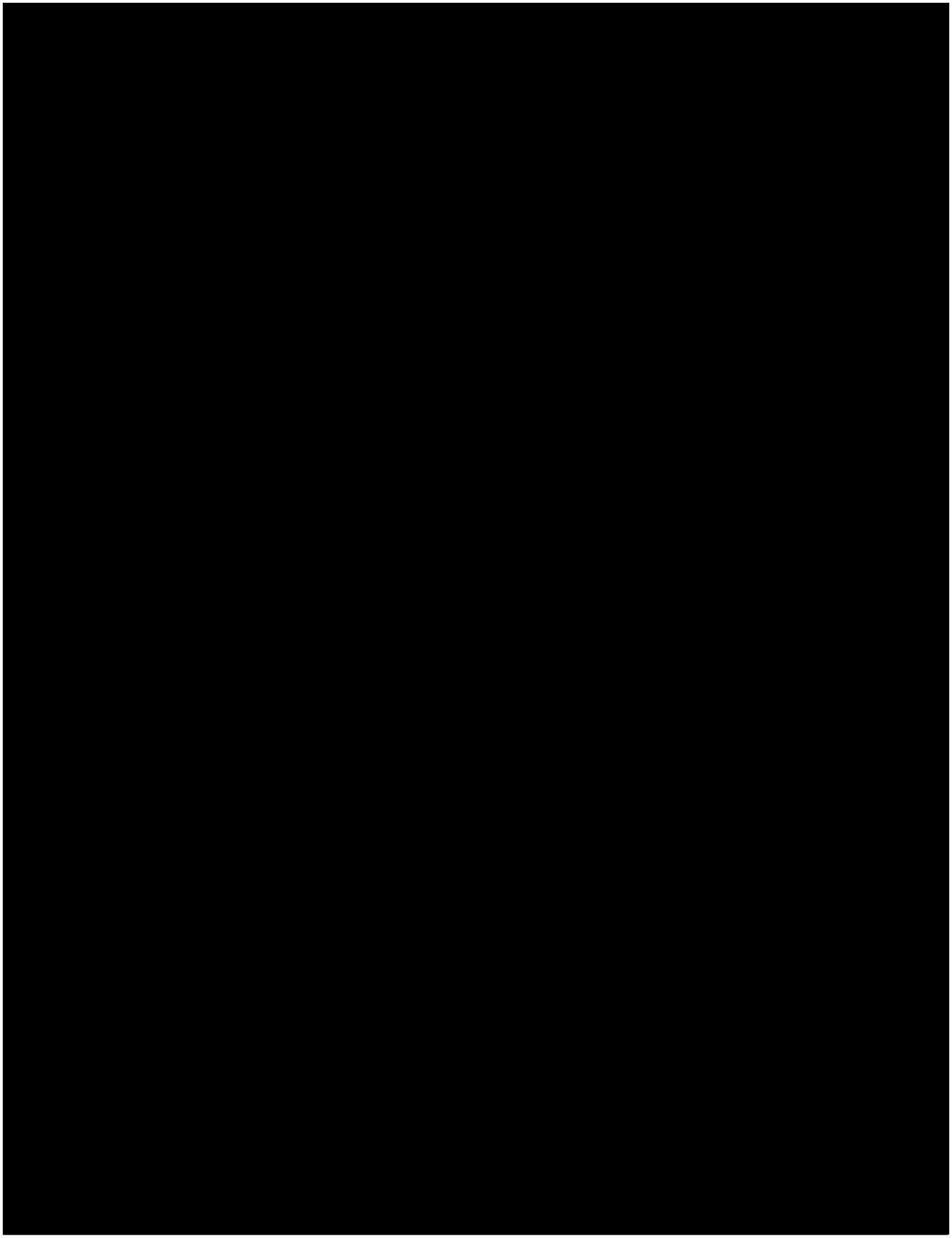
[redacted]

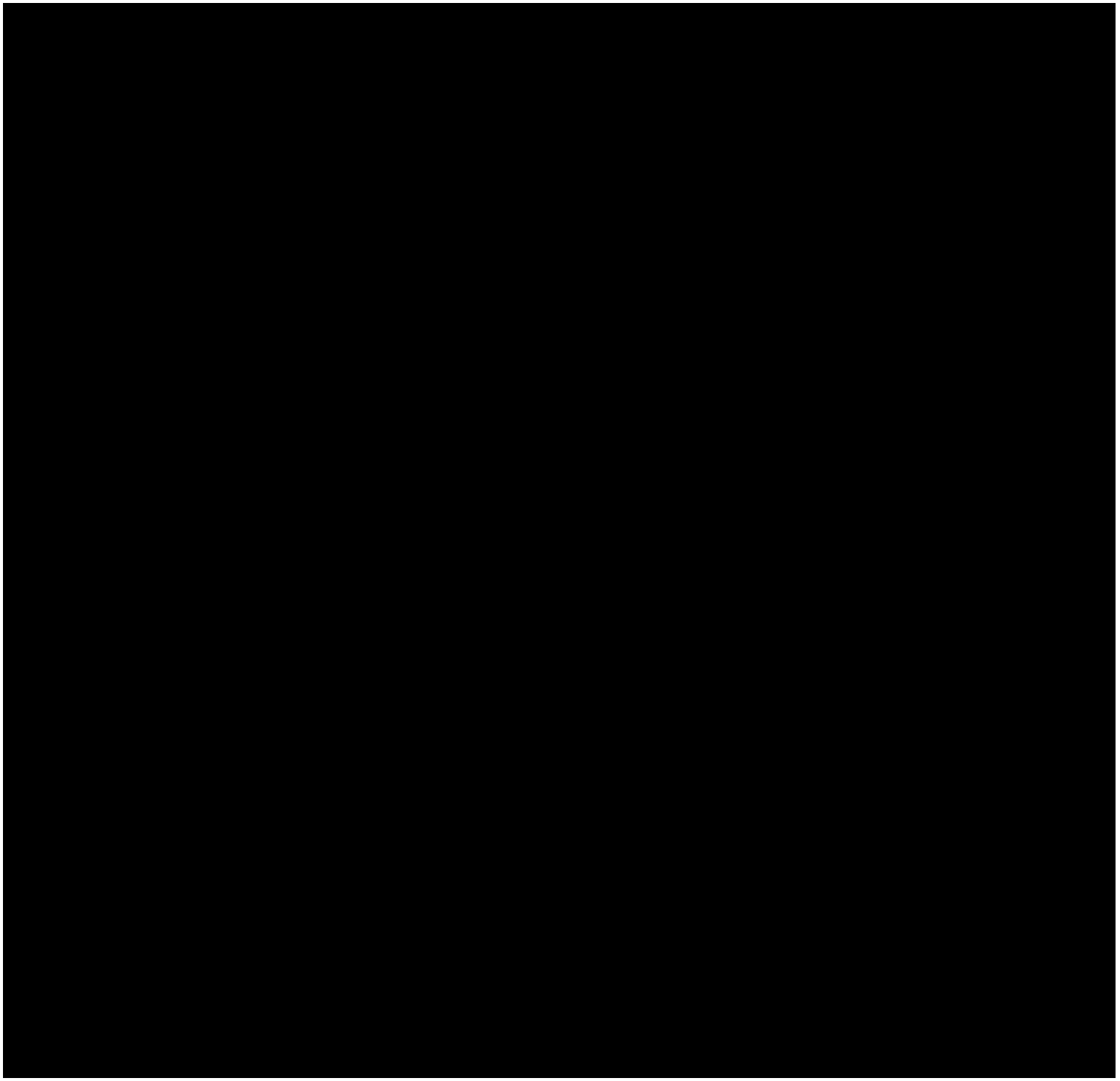


[redacted]









[redacted]